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DEPARTMENT OF DEFENSE

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# **MILITARILY CRITICAL TECHNOLOGIES**

## ***PART III: DEVELOPING CRITICAL TECHNOLOGIES***

### ***SECTION 3: BIOLOGICAL TECHNOLOGY***



**July 1999**

**Defense Threat Reduction Agency  
Dulles, VA**

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## SECTION 3. BIOLOGICAL TECHNOLOGY

### *Scope*

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### **OVERVIEW**

The rapid growth of biotechnology since 1970 has provided many items and systems that are useful to the civilian and the military sectors. These products and processes relate to improvements in human health by production of new pharmaceuticals, including antibiotics, vaccines, and performance sustainers. Sensors capable of detecting infectious agents, toxins, and chemical agents have been developed and miniaturized using insights provided by biotechnology. During the past decade, innovations in monitoring human performance, vigilance, and fitness for duty have emerged from the use of imaging systems that permit viewing brain activity on-line and correlating the electrophysiological activity of the brain with human performance. Advances in genetic engineering, molecular biology, and polymer chemistry have created new opportunities in the fabrication of electronic circuits, molecular motors, and structures having high strength and low weight. The shelf life and palatability of foods has been markedly improved by discoveries in biotechnology.

The rapid growth in all these areas has been accompanied by federal and private sector investment in the United States and other developed nations. Some of this advanced technology has been acquired by developing nations, including those hostile to U.S. interests, potentially enabling adversaries to diminish the superior military capability of U.S. forces. This section describes the developing biotechnologies anticipated to be realized in a 20-year time frame. The roles of biological systems in the production of electrical energy are included in the Energy Technology section of Part III of the Militarily Critical technologies List (MCTL).

The rate of economic growth of the biotechnology industry is the most rapid of all industrial sectors, and this reflects the perceived importance of this industry on product development, processes, and systems. Between 1996 and 1997, the market capitalization of this industry increased 60 percent—from \$52 to \$83 billion. The revenues increased 15 percent, and the sales increased 16 percent. The largest applications of medically related biotechnology were in the United States.

### *Highlights*

- Biotechnology has sustained a growth rate of doubling the base of knowledge every 18 months to 2 years. This trend appears to be accelerating in the human genome, multi-array sensor, and biomaterials areas.
- The economic engine for biotechnology is the non-military commercial sector, including medicine/health, agriculture/food processing, cosmetics, and transportation.
- Military exploitation and harnessing of biotechnology is in the embryonic stage. The impact on the military is anticipated to be pervasive and fundamental in the areas of human performance, sensors, biomaterials/nanofabrication, and individual and group performance.
- Significant advances in biotechnology capabilities should be anticipated from developed and less-developed nations.

Each of the technology items identified in this section is being driven by broad requirements and applications. All are expected to develop a substantial set of non-military commercial applications and attendant manufacturing and support infrastructures. The industrial sectors supporting the biotechnology thrusts include health/medicine, pharmaceuticals, agriculture/food processing, and transportation. The military utility of specific biotechnologies for applications in national security systems has not yet been fully explored and developed.

### **RATIONALE**

In this section, the developing technologies have been categorized into four groups:

1. Human Performance Enhancement
2. Biological Sensors
3. Biomaterials and Nanofabrication
4. Individual and Group Protection.

These categories reflect the proposed and actual military application suggested in the Joint Vision 2010 documentation and the supporting Service planning guidance. Table 3.0-1 provides a matrix of the 22 developing technologies and identifies where they are covered within the four technology areas.

**Table 3.0-1. List of Developing Technologies and Concepts by Technology Group**

Developing Technology	Technology Groups			
	Human Performance Enhancement	Biological Sensors	Biomaterials and Nanofabrication	Individual and Group Protection
A. Recognition/perception	X			
B. Memory	X			
C. Visual/auditory/olfactory	X			
D. Cognition	X			
E. Electrophysiological monitor and brain activity	X			
F. Brain imaging	X			
G. Human performance maximization	X			
H. Nanofabrication		X	X	
I. Sensors/molecular recognition		X		
J. Biomedical imaging and automation				X
K. Biomaterials		X	X	
L. Encapsulation		X		X
M. Human Genome Project	X			X
N. Pathogen Genome Project		X		X
O. Atomic Force Microscopy (AFM) and Near Field Scanning Optical Microscopy (NSOM)		X	X	
P. Increased disease resistance				X
Q. Thin films [charged-coupled device (CCD)]		X	X	
R. Microelectromechanical Systems (MEMS)		X	X	X
S. Blood substitutes and biocompatible clotting matrices				X
T. Locator of persons				X
U. Water purification	X			X
V. Biomarkers for toxicant/stress exposure	X			X

Table 3.0-2 identifies the military applications of these developing technologies. Appendix A supports these summary tables by showing the individual Service needs related to each of the identified biotechnologies.

Because the technology developments are funded primarily for dual-use pharmaceuticals, materials, and equipment, nations that currently possess leading-edge capabilities in biotechnology and the biosciences are anticipated to be the most economically developed nations with particular strength in pharmaceuticals, food processing, medical technology, and cosmetics. High-value-added products requiring these technologies are in the pharmaceutical, food, and cosmetic arenas. The rapid progress currently seen in the Human Genome Project is likely to give rise to an explosion of new products affecting human health, performance, and disease resistance. New diagnostic procedures for disease susceptibility and anticipated life-span enhancement will emerge. Since the sequencing of the genome of bacteria, viruses, and fungi is progressing at a high rate and results are correlated with genomic data from the Human Genome Project, the genetics of disease susceptibility in various human populations will emerge. A current example is the finding in 1998 that resistance to Human Immunodeficiency Virus (HIV) in persons of European ancestry is associated with resistance to plague developed in these populations during the epidemics of the 14th to 17th centuries. The genetic factors responsible for virulence of certain bacteria, viruses, and fungi are currently being identified, and the pathogenicity islands (PAIs) are being mapped.

#### ***WORLDWIDE TECHNOLOGY ASSESSMENT (See Figure 3.0-1)***

The Human Genome Project is an international effort with complete exchange of information and databases for humanitarian purposes. The development of multi-national industries in the area of biotechnology has increased markedly as a result of tax and tariff structures that favor such alliances. The international regulatory standards applied to pharmaceuticals, food, and biomedical materials further encourage international cooperation and technology transfer. The biological and biomedical sciences sections of graduate and postgraduate education in the United States have the highest numbers of foreign students. This reality alone enhances transfer of technology to all nations, particularly less-developed countries. The low economic cost required to establish biotechnology facilities should result in rapid transfer of production capabilities to countries that do not lead in technologies. Shipping costs and capital investment are minimal. Precursor material and end products are low in weight. Production is not capital intensive compared with silicon-based electronics and analogous processes. Figure 3.0-2 provides an estimate of the capability of the identified nations in the development of products using biotechnology as a means of production. Although the less-developed countries will be able to acquire these technologies, the time interval between

achieving production in the most advanced nation and least developed nation is anticipated to be on the order of 2 to 5 years.

Because of the breadth of effort and level of funding, the United States leads the rest of the world in aggregate discoveries and progress in biotechnology. However, other industrialized nations carefully track biotechnology progress through multiple open and corporate sources. The rapid dissemination of information through the world wide web and the rapid access of summaries of newly published articles through MEDLINE, Chemical Abstracts, and Science Citation Indexes increase the transfer of information across national borders at rapid rates. The delay between publication and appearance in electronic distribution is less than a month. Thus, the transition of a technology into products can be accomplished with equal speed in any relatively industrialized nation. Countries that have demonstrated such capability include China (for internal consumption), France, Germany Japan, Israel, Sweden, and the United Kingdom. Other nations, such as Switzerland, have moved extensive development and production facilities out of the country for economic reasons. Russia has a residual aggregate knowledge base from the days of the Union of Soviet Socialist Republics (USSR), and this is moderately enhanced by international partnering with industries in the United States and other nations. However, in Russia, the transition of the knowledge base into products continues to decline.

**Table 3.0-2. Developing Technologies and Concepts Related to Biological Systems**

<b>A. RECOGNITION/PERCEPTION</b> Grandmother cell Gamma phase 40 Hz Hebbian circuit	<b>F. BRAIN IMAGING</b> Magnetic Resonance Imaging (MRI) Functional MRI (fMRI) Positron Emission Tomography (PET) X-ray digital
<b>B. MEMORY</b> In vivo gene regulation (CREB)	<b>G. HUMAN PERFORMANCE MAXIMIZATION</b> Biological Response Modifier (BRM) as performance sustainer Drugs, diet, and equipment that sustain performance Analgesia without depression Pain control chemicals Circadian rhythm synchronizers Neuroprosthetics and chemicals (growth factors that enhance nerve repair) Exoskeletal supports Immune response enhancers
<b>C. VISUAL/AUDITORY/OLFACTORY</b> Visual perception HMD Visual display NVD Iconographic display 3-D display (audio, visual, tactile)—simulation and virtual reality Odor detectors Miniature auditory implant	<b>H. NANOFABRICATION</b> Protein/Lipid/Nucleic acid self assembly Switching devices (MEMS) AFM and NSOM devices
<b>D. COGNITION</b> Artificial intelligence Information warfare Axonal guidance-model for data fusion DNA computing	<b>I. SENSORS/MOLECULAR RECOGNITION</b> Dynamic interactive arrays based on antibodies, nucleic acid sequences, or receptors Swarm systems Human vital systems card (physiological/metabolic indicator; triage; alertness; and ID)
<b>E. ELECTROPHYSIOLOGICAL MONITOR AND BRAIN ACTIVITY</b> EEG Visual evoked potential Brain stem auditory evoked potential Eye movement	<b>J. BIOMEDICAL IMAGING AND AUTOMATION</b> Telemedicine—pod for rapid transport/containment of wounded Information systems—worldwide current status of infectious diseases Medical history of personnel on card Train and assist Corpsmen by telecommunication Distributed decision-making Integrate medical into C2 architecture

**Table 3.0-2. Developing Technologies and Concepts Related to Biological Systems (Continued)**

<p><b>K. BIOMATERIALS</b></p> <ul style="list-style-type: none"> <li>bacterial Rhodopsin</li> <li>phthalocyanine</li> <li>Bioceramics</li> <li>Body armor and personal protective systems</li> <li>Neuronal assemblies on chip</li> <li>Molecular switches (see Technology Item H)</li> <li>Blood substitutes (see blood substitutes (see Technology Item S)</li> <li>Molecular motors (MEMS—see Technology Item R)</li> </ul>	<p><b>Q. THIN FILMS (CCD)</b></p> <ul style="list-style-type: none"> <li>Artificial retina</li> <li>Information storage</li> </ul>
<p><b>L. ENCAPSULATION</b></p> <ul style="list-style-type: none"> <li>Vaccines</li> <li>Performance enhancers</li> <li>Food materials and nutrients</li> </ul>	<p><b>R. MICROELECTROMECHANICAL SYSTEMS (MEMS)</b></p> <ul style="list-style-type: none"> <li>Switching devices</li> <li>Sensors</li> </ul>
<p><b>M. HUMAN GENOME PROJECT</b></p> <ul style="list-style-type: none"> <li>Determine susceptibility of human populations to disease</li> <li>Determine genetic susceptibility of individuals in military to toxicants, resistance to infectious diseases and sleep deprivation, and stress. All these are components of allelic profiling.</li> <li>Drug design</li> </ul>	<p><b>S. BLOOD SUBSTITUTES AND BIOCOMPATIBLE CLOTTING MATRICES (see Technology K)</b></p> <ul style="list-style-type: none"> <li>Topical Fibrin</li> </ul>
<p><b>N. PATHOGEN GENOME PROJECT</b></p> <ul style="list-style-type: none"> <li>Pathogenicity islands (PAIs)</li> </ul>	<p><b>T. LOCATOR OF PERSONS</b></p> <ul style="list-style-type: none"> <li>Transmitter</li> <li>Excreted biocompatible material in urine</li> </ul>
<p><b>O. ATOMIC FORCE MICROSCOPY (AFM) AND NEAR FIELD SCANNING OPTICAL MICROSCOPY (NSOM) (see Technology Item I)</b></p> <ul style="list-style-type: none"> <li>Nanoscale manufacture quality control</li> </ul>	<p><b>U. WATER PURIFICATION</b></p> <ul style="list-style-type: none"> <li>Fluid capture and retention</li> </ul>
<p><b>P. INCREASED DISEASE RESISTANCE</b></p> <ul style="list-style-type: none"> <li>Super vaccine</li> <li>Recombinant vaccines</li> <li>Inhibit virus entry, intracellular transport, and maturation necessary for viral infectivity</li> <li>Multi-component, multi-valent vaccination</li> <li>Novel antibiotic with restricted distribution</li> </ul>	<p><b>V. BIOMARKERS FOR TOXICANT/STRESS EXPOSURE</b></p> <ul style="list-style-type: none"> <li>Glutathione S transferases</li> <li>P450</li> <li>Acute phase proteins</li> </ul>

**Note for Table 3.0-2:** The bolded categories identify the developing technologies. The concepts under these categories provide examples of specific elements/applications of the technology.

Country	Human Performance Enhancement	Biological Sensors	Biomaterials and Nanofabrication	Individual and Group Protection
Australia	●●●	●●●	●●	●●
Canada	●●●	●●●	●●●	●●●
China	●●	●●	●●	●●
Cuba	●	●●	●	●●
Czech Republic	●●	●●●	●●	●●
Egypt	●●	●	●	●
France	●●●	●●●●	●●●●	●●●●
Germany	●●●	●●●●	●●●●	●●●●
Hungary	●●	●●	●●	●●
India	●●	●●	●●	●●
Iran	●	●	●	●
Iraq	●	●	●	●
Israel	●●●	●●●	●●●	●●●●
Italy	●●●	●●●	●●	●●
Japan	●●●●	●●●●	●●●●	●●●
Malaysia	●●	●	●●	●
Netherlands	●●●●	●●●●	●●●●	●●●●
North Korea	●	●	●	●
Norway	●●●	●●	●●	●●
Poland	●●	●●	●●	●●
Russia	●●●	●●●●	●●●	●●●
Singapore	●●	●●	●●	●
South Korea	●●	●●●	●●	●●
Sweden	●●●	●●●●	●●●●	●●●●
Switzerland	●●●●	●●●●	●●●●	●●●●
Syria	●	●	●	●
Taiwan	●●●	●●●	●●●	●●
Ukraine	●●	●	●	●●
United Kingdom	●●●●	●●●●	●●●●	●●●●
United States	●●●●	●●●●	●●●●	●●●●

Legend: Capability in Technology Elements: ●●●● Most ●●● Many ●● Some ● At Least One

Figure 3.0-1. Biological Technologies Area Worldwide Capability Assessment

## SECTION 3.1 HUMAN PERFORMANCE ENHANCEMENT

### OVERVIEW

In the future, one of the most significant applications of emerging biotechnologies will be to enhance operational warfighter performance by improving perception, information processing, decision-making, and task execution capabilities. For the Militarily Critical Technologies List (MCTL), biotechnology can be used to increase these facets of human performance in three areas:

- **Physiological monitoring.** Psychological monitoring technologies, using miniaturized electrodes and data fusion systems that require low energy, will detect and assess changes in warfighter cardiovascular and neurological processes in real-time to drive system adaptation.
- **Information display and control.** Information display and control technologies will present and organize information or control systems to optimize warfighter awareness, decision-making, workload, and reaction times.
- **Pharmacological intervention.** Pharmacological intervention technologies, such as drugs or environmental changes, will improve the physiological processes underlying warfighter performance.

These areas will provide for the prescreening of personnel to determine genetic and non-genetic prognosticators that may indicate a susceptibility to stress and toxicants and for the analyses of paradigms for complex behaviors involving swarms and hives. If successfully pursued, these areas will be critical in maintaining and increasing our military superiority.

### RATIONALE

The soldier is the basic unit of the combat force. The intrinsic nature of the person and the training, equipment, and support components provided are decisive elements in determining success in military operations. In this decade, it will be possible to understand the genetic basis of human function. As a result, it may become possible to determine how the individual soldier is likely to respond to chemical and biological threats and other fear-inducing situations. The particular susceptibility of individuals to specific biological agents may be able to be determined. It is also likely that new vaccines and therapies will be developed to help cope with threats in the environment. Knowledge of the individual susceptibility to disease and the mechanisms by which such susceptibility can be managed are critical to the

#### *Highlights*

- Selection of personnel for task suitability will become increasingly accurate and sensitive based on identification of specific biomarkers for toxicant susceptibility, stress, and sustained performance.
- Performance monitoring and warning will enhance the ability of the military cohort to sustain and maximize mission goals of individuals and teams.
- Pharmacological intervention will enable military units to extend and sustain effective operational capabilities.

maintenance of force structure and mission success. This awareness is even more essential as the number of people engaged in military actions is reduced and the active duty forces are requested to participate in an increasing number of police actions.

New technologies have also increased our understanding of the way in which humans respond to information. Iconographic displays associated with auditory and haptic information markedly reduce the time required to detect a change in the environment that may be hazardous (e.g., the spatial location of an incoming air-to-air missile or the direction of fire). Distributed information systems have enabled modeling of combat or rescue scenarios before the actual mission and have improved the identification of potential threats in a given setting.

Interfacing the human genome database with computer-assisted perception will prepare the soldier and the command for threats in a particular setting and, thereby, improve mission performance.

### TECHNOLOGY DESCRIPTIONS

#### *Physiological Monitoring (Technology Items A,B,C,D,E,F,G,M,V in Table 3.0-2)*

Technologies that can non-obtrusively measure core physiological processes in a military environment are evolving. Applied research is successfully producing models that use those measures to determine operator cognitive workload, vigilance, and fatigue reliably in order to drive task allocation between the operator and the system

or change information presentation to capitalize on available resources. The physiological parameters that can be correlated with functional performance changes include auditory and visually evoked potentials, broadband brain activity (e.g., using complex electroencephalographic output with an extended numbers of channels), eye movements, heart interbeat intervals, respiration rates, and blood oxygen levels. Imaging technologies, especially functional Magnetic Resonance Imaging (fMRI), Positron Emission Tomography (PET) using  $^{15}\text{O}$  or  $^{18}\text{F}$  labeled derivatives, and magnetoencephalography, can reveal brain areas that are active during specific tasks.

These technologies promise real-time analyses of performance for automation decisions or rapid screening tools for measuring job fitness. Interpretation of EEG-monitored brain wave patterns to indicate intended operator actions will occur on-line with near instantaneous reaction times and will allow the elimination of motor response errors (termed “brain activated control”). Technologies requiring physiological inputs, such as brain activated control, will capitalize on the development of remote (i.e., non-contact) sensors and analytical tools like fMRI. In addition, physiological changes could be inferred from changes in task accomplishment or loading by using models of human performance. Monitoring operator state for impending unconsciousness will serve to ensure safety by permitting the automatic transfer of operator control to the system computer.

The exposure of warfighters to common physiological stressors, such as toxic chemicals, sleep deprivation, jet lag, and anxiety, can result in both acute performance decrements (like reduced vigilance or fatigue) and chronic health problems (generally resulting from an immuno-suppression that increases susceptibility to diseases of the nervous system, liver, and lungs). Today, the military can identify an affected individual only after his performance has been critically impacted. By that time, simple interventions are usually too late to correct mission performance or prevent disease. Military readiness could be improved dramatically by tracking physiological measures that can provide an early warning of impending performance problems. The biochemical markers of acute exposure to stress include the enzymes glutathione S-transferases and cytochrome P450. Biomarkers that reveal longer term exposure to conditions that compromise function or lead to unacceptable risk for error in highly skilled individuals are also of critical importance. Recent advances in the behavioral sciences, neurophysiology, biochemistry, medical imaging, and ergonomics provide the opportunity for developing early physiological monitoring techniques to detect situations that will degrade human performance. The development of unobtrusive monitors for these early warning markers will increase the likelihood of effective performance and reduce the risk of failure. A substantial improvement in the effectiveness of weapon systems that depend upon human interactions for success can then be realized. These capabilities will have classic and multiple dual-use applications and linkages across large industries.

### ***Information Display and Control (Technology Items C,D,G in Table 3.0-2)***

In the realm of biotechnology, the presentation of information or the employment of control modalities can be designed to capitalize on specific interactions with human perceptual, cognitive, or motor systems. It can be expected that the human-machine interface will be incrementally transformed into an interactive fusion that is driven by changes in neurophysiological states.

The modeling of human information processing will be precise enough to design truly intuitive interfaces and to delineate the differences between computer and human information processing in order to optimize human-machine interactions and the allocation of mission functions. This improved understanding of mental processes will lead to enhanced situational awareness and decision-making by fundamentally changing the structuring of information interactions. Real-time monitoring of operator cognitive and perceptual resource consumption (i.e., workload), coupled with performance measures, will tailor information formatting to sensory modality and the assignment of tasking between the human and machine. This will provide a set of new boundaries in human information processing tailored to the individual performer.

Changes in information display and system control technologies will revolutionize the human-machine interface. Binocular, full color, wide field of view helmet mounted displays (HMDs) will integrate sensor and data fusion symbology into the visual scene and employ eye-tracking technology to allow extremely fast and accurate target designation, even at night. Thin films of biomaterial or biomimetics on the HMD may provide the visually detected data and symbology (see Biomaterials). Three-dimensional (3-D) audio and haptic interfaces will significantly decrease reaction times by providing redundant target localization cues. Robust speech recognition, developed at General Motors and Delco, will permit hands-off operation, even under the most stressful conditions. Significant decreases in material weights will decrease the fatigue and muscle strain associated with current systems. Together, these technologies will create a true virtual environment capability to allow windowless vehicles (e.g., Citadel Ships) or optimized remote control.

The development of virtual audio, visual, and haptic realities and the emerging networking of multiple and diverse systems allow many individuals to interact at remote stations. These technologies provide new opportunities for training skilled personnel, planning and testing responses to crisis situations, developing new operational strategies, conducting mission rehearsals, and evaluating the proposed solutions in low risk environments. This multi-system approach, using virtual realities and remote interactive systems, is the basis of advanced distributed simulation (ADS). A support system infrastructure for developing standards to be used in ADS has been created and is called distributed interactive simulation (DIS). DIS exercises support a cluster of virtual entities (human-in-the-loop simulators), live entities

(operational platforms and test/evaluation systems), and constructed entities (automated simulations).

#### ***Pharmacological Intervention (Technology Items A,B,C,G,M,U in Table 3.0-2)***

In the future, pharmaceuticals or manipulations of the environment will be used routinely to increase the cognitive and physical prowess and endurance of U.S. warfighters. This section provides a sampling of the expectations for military medical interventions to maximize performance.

The nature of the biological mechanism that allows a person to discriminate a subject cognitively from its background has been termed the “binding problem.” Currently, two fundamental theories address the binding problem:

- There exist nerve cells that store all the collective neural inputs for a solitary object through unique neurons (e.g., a cell that is used to recognize “grandmother”). Accordingly, different “grandmother cells” would be required for recognition of all items in long-term memory.
- There exist gamma phased 40-Hz circuits that are programmed to become activated when a target to be recognized appears. Sets of individual 40-Hz circuits may collectively comprise Hebbian circuits. If the memory is comprised of 40-Hz circuits, the introduction of selective 40-Hz signals from external sources may stimulate or suppress the memory system.

Evidence exists to support each of these physiological processes in different scenarios. The next decade is likely to see novel approaches to the design of pharmaceuticals that can enhance recognition speed and accuracy. Compounds, such as AMPAkinases, that increase both working and long-term memory functions will significantly improve warfighter situation awareness, decision-making, and task execution under stress.

The response of the warfighter to the battlefield environment is determined by training, physiological factors (e.g., strength and age), and the genetic factors of the combatant. The advent of the 21<sup>st</sup> century will provide increased information on the genetic contribution to the effectiveness of the warfighter. The sequencing of the entire human genome is expected to be complete by 2005. The genome will be characterized by rapid gene sequencers. One system in development prepares 400,000 bases per hour and analyzes about 8,000 bases per 16 hours. This system can determine the sequence of about 2 million bases per several months. A second strategy uses variants of mass spectrometry to sequence DNA. Matrix-assisted laser desorption ionization (MALDI) mass spectrometry has proved to be an important tool in synthetic- and bio-polymer characterization. The molecular sizes that can be sequenced by this technique are limited in 1997, but the method currently has utility for determining mutation sites in DNA fragments. The information to be obtained

from characterization of the human genome is likely to provide an understanding of performance, vigilance, and susceptibility to disease.

Classical gene therapy approaches allow new genes or functions to be introduced into cells or individuals to correct genetic disorders. While optimal vehicles for gene therapy still need to be developed, this limitation is likely to be solved in the foreseeable future, opening the way to many applications. In addition to correcting genetic defects, the same technology could be used to enhance performance or allow new capabilities. An extension of this notion is the use of similar technological approaches to control specific genes—turning them on or off at particular times. As one example, many of the genes responsible for programmed cell death (apoptosis) have been identified. Selectively altering their expression could greatly extend the life of desired cells or help to prevent their premature death, and, in combination with use or expression of growth factors, make possible selective growth control and controlled tissue regeneration.

Combinatorial genomics has also recently been developed. Similar in concept to combinatorial chemistry, this technology shuffles portions of genes to give a vast number of new combinations, which are then screened for a desired function. Enhanced function, or even new functions, can be generated by repeating the cycle many times to “evolve” optimized recombinants in vitro.

Research characterizing the expression of specific genes has determined that several genes, most notably the cyclic AMP-response element binding protein (CREB) gene, have products that enhance memory function in humans. The binding protein may be regulated by phosphorylation. As the human genome is further characterized, it is likely that other gene products will be associated with memory. Knowledge of the gene sequence can facilitate the development of drugs that interact with critical regions of the gene to increase production of proteins that enhance memory. Conversely, anti-sense molecules that effectively block proteins that diminish memory may be developed. The analyses of the genome of people with senile dementia or Huntington disease may reveal the existence of gene products that compromise memory.

As the number of military members shrinks but the number of deployments increase, the force that can be maintained will depend to a great extent on how well individuals can be protected from the effects of sustained operations—most notably fatigue, sleep loss, and circadian desynchronization. For example, replacement or additional personnel may not be available. Consequently, sleep will be sacrificed to extend duty times. When sleep time is available, it will often be fragmentary, and people will be expected to perform their missions immediately upon awakening. The detrimental impacts on mission performance are obvious. For example, 15 percent of mishaps in naval combat aircraft and 13 percent of the associated deaths can be attributed to sleep deprivation, fatigue, and/or circadian disruption. In a study of

friendly fire casualties, most of the causal errors could be attributed to the negative consequences of sleep deprivation on operator performance.

Increasing knowledge about the hormonal and neurochemical basis of circadian rhythms and their role in memory, vigilance, decision-making, and other cognitive functions will lead to meaningful drug interventions. Under normal conditions, circadian rhythms are entrained to approximately 24 hours by the presence of a number of Zeitgebers (i.e., environmental events that provide the stimulus setting the biological clock), such as the occurrence of light and dark, that inhibit or permit the release of melatonin, a hormone produced by the pineal gland. Strategies that use melatonin to induce sleep or shift circadian rhythms to negate jet lag or block melatonin (e.g., bright light) or to sustain arousal will enhance performance during time zone transitions. Improvements (up to threefold increases) in the duration of effective duty times (up to 72 hours) and recovery from sustained operations will be made possible by fatigue management through pharmacological interventions (e.g., ergogenic compounds) that either induce sleep and circadian synchronization or produce controlled arousal through targeting neural center stimulation and inhibition (e.g., modafanil) without side effects. Administration of these pharmacological controls will be individually titrated to the needs of the warfighter through next-generation drug delivery systems.

#### ***TIMELINE FOR TECHNOLOGY AVAILABILITY***

Predicting when specific human performance enhancement technologies will be routinely available to the warfighter is difficult because gradations of capability will be introduced progressively. This notwithstanding, projections for the near term, midterm, and far term can be made with some confidence. Near term implies 3 to 5 years, midterm implies greater than 5 years but less than 10 years, and far term implies greater than 10 years. The application of perception and cognition research to the design of intuitive interfaces, automation, and decision-making will begin in the near term; some real-time, rudimentary physiological monitoring that drives meaningful changes in task allocation will be available in the midterm; and true system fusion and, later, control of systems by thought will be available in the far term. Revolutionary changes in the human systems interface will appear at the end of the near term or in the midterm. Significant pharmacological interventions to manage fatigue will begin in the next few years; however drugs or gene products that will change memory, for example, will appear in the midterm.

#### ***ADDITIONAL DATA***

Tables 3.1-1A and 3.1-1B present additional data on this developing critical technology.

#### ***WORLDWIDE TECHNOLOGY ASSESSMENT (See Figure 3.1-1)***

Those nations that have advanced human genomics and strong human behavior research efforts are leaders in this area. The Human Genome Project is a multi-national effort, with leading contributions from France, Japan, the United Kingdom, and United States. Since the genomic information is the result of a multi-national effort and the data are placed on the world wide web, most nations have ready access to the results. The methods used to transition these data to useful information resides in the laboratories in which the data are acquired. The human behavior research programs of Germany, the Netherlands, and the United States have been at the leading edge. Much of the equipment used to collect electrophysiological data related to human perception and response is used in the medical community. The information obtained from these studies has applicability for improvement of performance in the transportation, medical, manufacturing sectors and in the military. Germany, Japan, the Netherlands, and the United States have strong programs in information display and control. Pharmacological intervention expertise is reflected in development and production facilities in France, Switzerland, the United Kingdom, and the United States.

**Table 3.1-1A. Human Performance Enhancement Militarily Critical Technologies**

<b>Technology</b>	<b>Developing Critical Technology Parameter</b>	<b>Rationale</b>	<b>Critical Materials</b>	<b>Technical Issues</b>	<b>Joint Vision 2010 DoD S&amp;T Plan</b>	<b>Unique Test, Production, and Inspection Equipment</b>
<i>Miniaturized, non-obtrusive measures of eye movements; auditory- and visual-evoked potentials; EEG; cardiac interbeat interval; oxygen saturation</i>	Drowsiness indicator; vigilance and fitness monitor; physiological indicators that predict decreased combat performance. Miniaturized auditory evoked potential in the 300-ms wave and visual in the 300- to 600-ms wave.  Application ready in near term to midterm for evoked potential and eye movement.	Real-time assessment of operator workload, vigilance, and fatigue to drive adaptive automation and information formatting will maximize human system interface and safety. Provides human and automated intervention capability to assess and support vigilance and operational readiness.	Miniaturized sensors embedded in body cover or helmet; lightweight data fusion tools and energy-efficient signal transmissions.	Determination of reliable, useful correlations between physiological measures and measures of cognitive performance and combat readiness.	Information and systems integration; dominant battlespace awareness; dominant maneuver; agile organization training.  See Table A-7.	None identified.
<i>Functional MRI</i>	Simulator training with fMRI correlates brain functional response to training to job criteria. Magnet level of 1.8 Tesla or higher.	fMRI enables evaluation of training by examining anticipated movement (intent before action).	Non-magnetic simulator system required to use MRI.	Long-term fMRI (time longitudinal map) will resolve baseline variations.	See Table A-7.	None identified.
<i>Information display and control; robust voice control of military systems; 3-D audio/visual displays; brain activated control of machine interfaces; haptic interfaces; HMDs</i>	Interface-evoked potentials with human-machine interfaces and virtual reality projectors. Response times in 10 to 100 ms.	"Hands-free" task execution and localization cues from multiple sensory modalities decrease reaction times and enhance control by operator.	Integrated audio/visual/ haptic information presentation.	Development of multi-modal sensory presentation for all people. Development of interface to allow neural control of flight systems.  Application ready in near term.	Information integration; dominant maneuver; agile organization training; focused logistics; precision engagement.  See Table A-7.	None identified.

**Table 3.1-1A. Human Performance Enhancement Militarily Critical Technologies (Continued)**

<b>Technology</b>	<b>Potential Developing Critical Technology Parameter</b>	<b>Rationale</b>	<b>Critical Materials</b>	<b>Technical Issues</b>	<b>Joint Vision 2010 DoD S&amp;T Plan</b>	<b>Unique Test, Production, and Inspection Equipment</b>
<i>Pharmacological interventions, including drugs that affect object recognition and improve memory functions and drugs that control arousal or sleep and produce circadian synchronization</i>	Permits selective intervention in time-limited and reversible manner. Intervention is effective within minutes, and duration is hours.  A sustained high performance level, including sleep/work cycles synchronized to work demands.	Enhancement or degradation of memory will affect human performance of skilled tasks for C3 personnel, aircraft, or other complex systems.	Drugs that bind or otherwise affect CREB or offer AMPAkinases functions.	Development of drugs that bind selectively to memory-related genes or to receptors that are involved in sleep control.  Understanding the process underlying memory and maintenance and the differentiation of memory.	Dominant maneuver; precision engagement; full dimensional protection; full spectrum dominance.  See Table A-7.	None identified.
<i>Biomarkers for early detection of genetic susceptibility to toxicants and stress</i>	Rapid identification (in hours) of human genes affecting susceptibility to toxicants, stress, and disease. Includes genes for cytochrome P450, GST, acute phase proteins.  Application ready near term to midterm.	The human genome will reveal factors of susceptibility to toxicants and stress. Mutations affecting activity of toxicant metabolizing enzymes may result in increased susceptibility.	None identified.	Creation of a database relating human genome to toxicant and stress susceptibility.	Full dimensional protection.  See Table A-7.	None identified.
<i>Biomarkers for detection of environmental agents or conditions that adversely affect human performance</i>	Detects body response to and insulate from toxicants that degrade human performance in either or both near term (minutes to hours) and long term (years). Glutathione transferases and cytochrome P450 are detector biomolecules.  Application ready near term to midterm.	Rapid increases in the levels of these biomarkers may provide early warning of performance degradation.	None identified.	Determination of specific environmental factors that adversely affect human performance.  Determination of specific physiological indicators that predict decreased human performance.	Full dimensional protection.  See Table A-7.	None identified.

**Table 3.1-1B. Human Performance Enhancement Militarily Critical Technologies**

<b>Technology</b>	<b>Military Applications</b>	<b>Unique Software</b>	<b>Center of Technology Development: Military or Commercial</b>	<b>Commercial Applications</b>	<b>Commercial Technology Requires Development for Military Use</b>	<b>Access To Technology</b>	<b>Other Important Data</b>
<i>Miniaturized, non-obtrusive measures of eye movements; auditory- and visual-evoked potentials; EEG; cardiac interbeat interval; oxygen saturation</i>	Provides indicators of loss of vigilance and fitness and predicts decreased combat performance and readiness.	Signal-averaging miniaturization and data-sorting algorithms and programs.	Multiple commercial development centers include assessing production line assessments in factories; determining effectiveness of the medical care delivery (e.g., surgery); assessing human monitor of chemical process production (petroleum industry); measuring fitness of pilots and railway engineers; monitoring patients.	Provides equivalent indicators of loss of vigilance and fitness and predicts decreased performance and readiness in industry and commerce.	Commercial applications drive technology in biomedical arena. Leading-edge R&D is commercial.	Ready access for the military. Some proprietary issues apply.	None identified.
<i>Functional MRI</i>	Ensures performance in stress conditions, with correlation of brain and behavior functions.	None identified.	Training centers for airline pilots and railway engineers; medical monitors for patient status.	Diagnosis of disease in patients. Training for high-skilled jobs.	None identified. Still in development.	Ready access.	None identified.
<i>Information display and control; robust voice control of military systems; 3-D audio/visual displays; brain activated control of machine interfaces; haptic interfaces; HMDs</i>	Decreases response time under stress of battle; SUSOPS; informs operator of direction of target or incoming missile by multiple modalities; optimizes man-in-the-loop cognitive and motor workload and tasking.	Software for interfaces.	Biomedical applications in operating rooms for anesthesiology; precision machining of production processes involving toxic/radioactive materials.	Decrease response time under stress; motor workload and tasking; enhance performance in variable shift work.	Commercial applications drive the technology.	Ready access.	None identified.

**Table 3.1-1B. Human Performance Enhancement Militarily Critical Technologies (Continued)**

<b>Technology</b>	<b>Military Applications</b>	<b>Unique Software</b>	<b>Center of Technology Development: Military or Commercial</b>	<b>Commercial Applications</b>	<b>Commercial Technology Requires Development for Military Use</b>	<b>Access To Technology</b>	<b>Other Important Data</b>
<i>Pharmacological interventions, including drugs that affect object recognition and improve memory functions and drugs that control arousal or sleep and produce circadian synchronization</i>	Reduces training time; enhances situation awareness; improves reaction time; improves decision-making under stress; enhances fatigue management; SUSOPS.	None identified.	Military may drive selective use of drugs that enhance vigilance for 72 hours. Military will want to develop counter-measures for drugs that disrupt memory processes.	Training people for complex tasks; treating learning disabilities (e.g., ADD).	The commercial and military world have complementary needs.	Ready access to drugs for learning enhancement.	None identified.
<i>Biomarkers for early detection of genetic susceptibility to toxicants and stress</i>	Selection of soldiers for DECON and for TADMUS activities.	Database of human genome.	The medical and pharmaceutical industry and NIH fund 90 percent of this activity.	Assisting with liability assessment; enhancing biomedical diagnostics.	Commercial sector drives technology.	Ready access to human genome.	See Biomedical Section, Part III of MCTL. Ethic and privacy cultural issues involved.
<i>Biomarkers for detection of environmental agents or conditions that adversely affect human performance</i>	Enables proactive avoidance of hazards; creates opportunity to detoxify.  Increases avoidance of threat situations; assists in implementation of strategies to improve mission outcome.	Database of correlative information.	Industrial hygiene; OSHA and industrial liability concerns have interest.	Improving safety of workplace and reduce liability.	Private sector and NIH are major supporters of technology development.	Ready access.	None identified.

Country	Physiological Monitoring	Information Display and Control	Pharmacological Intervention
Australia	●●●	●●	●●●
Canada	●●●	●●●	●●●
China	●	●	●●
Cuba	●	●	●●
Czech Republic	●●	●●●	●●
Egypt	●●	●●	●●
France	●●●	●●●	●●●●
Germany	●●●	●●●	●●●
Hungary	●●	●●●	●●
India	●●●	●●●	●●
Iran	●	●	●
Iraq	●	●	●
Israel	●●●	●●●	●●●●
Italy	●●●	●●	●●●
Japan	●●●	●●●●	●●●●
Malaysia	●●	●●	●●
Netherlands	●●●●	●●●●	●●●
North Korea	●	●	●
Norway	●●	●●	●●●
Poland	●●	●●	●●
Russia	●●●	●●●	●●●
Singapore	●●	●●●	●●
South Korea	●●●	●●●	●●
Sweden	●●	●●●	●●●●
Switzerland	●●●●	●●●●	●●●●
Syria	●	●	●●
Taiwan	●●●	●●●	●●●
Ukraine	●●	●	●
United Kingdom	●●●●	●●●●	●●●●
United States	●●●●	●●●●	●●●●

**Legend: Capability in Technology Elements:** ●●●● Most ●●● Many ●● Some ● At Least One

**Figure 3.1-1. Human Performance Enhancement Technologies Area Worldwide Capability Assessment**

## SECTION 3.2 BIOLOGICAL SENSORS

### OVERVIEW

A sensor provides the interface through which a system can detect the state of a changing environment in real time. It can also provide information about the interaction between the environment and individuals. Appropriate sensors and data fusion systems serve to integrate operational systems in much the same way as the sensory nervous system in the body. This analogy has given impetus to the construction of multi-spectral [shark-electromagnetic detection; pigeons and ultraviolet (UV) detection; swine and canine odor detection] and non-traditional (abiotic “sensored” insects) sensors for scanning the battlefield and for force deployment. The integration of advances in optics, electronics, microfabrication technology, and molecular biochemistry has made biosensor technology an area of rapid technological progress. Concepts that will result in improved field sensors by the year 2010 include gene probes, monoclonal and genetically engineered antibodies and other receptors, high-precision polymer molding, polymer liquid crystals, chemiluminescence, neuronal and protein DNA patterning, combinatorial chemistry, monolithic UV/visible/infrared (IR) laser light-emitting and light-detecting surfaces, Microelectromechanical Systems (MEMS), charge-coupled devices (CCDs), and neural networks.

At present and, in fact, in our entire history of chemical syntheses, it is estimated that less than 1 percent of all possible organic compounds have been synthesized. Combinatorial chemistry uses automated production and screening of thousands of compounds, typically for drug screening or for materials with novel electroconductive properties. The number of compounds that can be synthesized per day is now in the thousands, and the production size is growing. One method produces as many as 25,000 different substances on a 3-inch diameter substrate. The challenge of this technology is to develop methods that rapidly screen the newly synthesized materials for properties of interest. Technologies for large-scale screening remain to be developed.

Advances in synthesis and screening will lead to very small, lightweight, energy-efficient biosensors capable of simultaneous analysis for multiple analytes. All sensors would be reduced to a card format and integrated into a single case. Individual sensors can be formatted with both the biodetection components and the optoelectronic sensing elements in micron-scale arrays. Microfluidics, data processing, data transmission/display elements, and electropower sources will be incorporated with the optical or electrochemical detector and the molecular or cellular biodetection components in a fully automated, hand-held unit. For automated

### *Highlights*

- Biological multi-array sensors will permit rapid and accurate acquisition, storage, and assessment of data for biological, chemical, and mechanical signals.
- Biological sensors are anticipated to be more compact, energy efficient, and sensitive than non-biological units.

environmental monitoring, these units will be adaptable to a variety of platforms. Materials that have applications in display technology can be rapidly screened. Corporations in the United States with technology in this area include Affymetrix and Symyx.

In addition, biosensors will be incorporated into suites of sensors. An example of such a suite would be an environmental monitor including sensors that measure meteorological conditions, Global Positioning Systems (GPSs), determinants for viability, UV-laser detectors for organic particles, generic biosensors for detecting any toxin or pathogen, and biosensors for biological agent identification. Data fusion techniques could assess the threat and deliver an assessment based on multiple factors. Similarly, a sensor suite for medical diagnostics could integrate sensors for temperature, blood pressure, pH, CO<sub>2</sub>, infectious agents, toxins, key enzymes, and markers of septic shock. Information acquired through the use of these sensors will markedly increase command and control (C2) awareness of the battlefield and other military environments.

In 10 to 30 years, these sensors and sensor suites will be “smart devices” that perform appropriate analyses, data fusion, and evaluation and then trigger an appropriate response, such as input to command. For instance, a sensor incorporated into a smart chemical and biological warfare (CBW) suit will close the suit’s pores in response to a chemical agent, activate the mask only in response to a biological agent, regulate internal temperature, and trigger the injection of antidotes after agent identification. For medical applications, the on-line monitoring of blood chemistries, endotoxins, and drug levels might automatically trigger the introduction of appropriate levels of therapeutic agents.

At the close of the 20th century, the U.S. defense community is experiencing a reduction in people and is conscious of the cost of acquisitions. The following subareas are critical to increasing military superiority:

- Molecular recognition components
- Biological and biomimetic photon and electron transfer materials
- Self-assembly systems, data fusion arrays, and characterization of the sensor surface.

Array sensors for enzymes, analytes, antigens, antibodies, receptors, and nucleic acid targets are available on chips that contain the biocomponents and the integrated circuitry to record the results. These arrays are supplied in the form of small disposable cassettes into which a sample of whole blood or any other biological fluid can be added. The “chip” will process the sample as required and move the processed material—through either capillary action or a small micropump—to the sites of analysis. The results could be read by the corpsman or telemetered to an off-site location for analysis and decisions regarding treatment and combat response.

Detection and measurement of infectious and toxic threats and of hazard substances can be done before and during deployment to any global location. Application of this sensor information is profound for the protection and functional well-being and mission accomplishment of deploying forces. See the Biomedical section in Part III of the MCTL.

## ***RATIONALE***

Sensors provide data regarding materials and conditions in the surrounding environment. Converting these data to information can enable the performance of many functions, including threat awareness, functional awareness of individual groups, awareness of selected field conditions, and readiness of equipment. Military implications include well-being of the soldier if taken ill or wounded and determination of CBW attack. A soldier may even be able to carry one of these devices as a dog tag that would notify a command center or central processor that this soldier has been exposed to an agent or other toxicant.

The most recent approaches have focused on exploiting the high affinity binding of naturally occurring molecules to target materials of interest. The molecules include polynucleotides that recognize pathogenic genome sequences of biological agents or human genomic material of interest; monoclonal and polyclonal antibodies that recognize surface molecules of biological or chemical agents; and receptors that change conformation following exposure to biological or chemical agents and generate an electronic or photonic signal.

The major element in the U.S. biological defense program is early detection, identification, and warning to provide situational awareness and allow military forces to avoid or manage the threat. Detection and identification of biological agents and the prediction of future threat situations provide useful information to military commanders and individuals. Such information permits the pre-treatment of people before deployment and the management of medical care following exposure

to infectious or toxic agents. The detection and identification of organisms in a deployed zone allow commanders to take steps to avoid contamination, determine the appropriate protection for continued operations, and initiate proper prophylaxis and therapy to minimize casualties and performance degradation. The appropriate care of the exposed people will increase the rate of their reinsertion into units and minimize long-term disability resulting from exposure to the agents. Biosensors based on genomics can rapidly distinguish pathogenic organisms and pathogen-producing organisms from non-pathogens.

## ***TECHNOLOGY DESCRIPTIONS***

### ***Molecular Recognition Components (Technology Items I,L,N in Table 3.0-2)***

Arrays based on antibodies, nucleic acid sequences, or receptors are in production at the close of the 20th century. Genomic sequencing of all known biological threat agents and infectious disease organisms is in progress. Some regions of the bacterial genome appear to be common among organisms pathogenic to humans (e.g., pathogenicity islands). Such regions could be used in detecting pathogens on nucleic acid arrays or other type of DNA/RNA detection systems. In addition, using anti-sense gene technology, stopping the pathogenic activity of an organism by tying up this region of the pathogens genome may be possible.

Nucleic acid oligomer arrays for the detection of specific gene sequences have been produced on patterned surfaces by Affymetrix, several other companies, and the Naval Research Laboratory (NRL). Similar arrays, for the sequencing of genes at very rapid rates to determine “viral load” and mutations, are being generated. Antibody and antigen arrays for detecting and quantifying biological agent antigens and antibodies that will permit the assay of several analytes simultaneously are in development. Sensors employing these components will allow the detection, characterization, and measurement of the concentration of biological agent and will predict the dispersal efficiency of the agent. Remote or standoff devices can be configured using this new technology.

This technology addresses real-world problems. Anthrax and other biological agents are normally present in particular environments. These agents vary in natural abundance as a function of geographical location, land use, season, and meteorological conditions. After a database has been established for natural abundance of each biological agent in a given setting, the multi-array sensor will inform the user when a threshold that requires action has been reached. This type of approach will be inexpensive, fast, and portable.

The application of receptors in analyses, as opposed to antibodies, is of great interest. Receptor- and antibody-based sensors are complementary and, in certain situations, may be useful together on an array. Antibodies provide information on

mass but not on biological activity. Ligand binding to receptors provides information on biological activity but not on mass. Military interests include an array that detects bacteria and bacterial toxins. Since putting genes for toxins in common organisms is possible, “hiding” the presence of a dangerous toxin from detection is possible. An array containing antibodies to the organisms, receptors to the active toxin, and gene probes for the toxins may recognize threat conditions earlier than any of the single-component sensors. Using MEMS technology, placing these arrays on the soldier and sharing the information through telemetry will be possible.

A Human Vital Systems Card is an example of an integrated biosensor and data fusion component. The devices use different technologies and perform different functions by measurement of parameters, such as  $pO_2$ ,  $pCO_2$ , pH, glucose, creatinine, blood urea nitrogen, blood electrolytes, and other components that would indicate the state of an individual. These devices can use MEMS and/or nanofabrication technologies and be small enough to be used either by being implanted under the skin or attached to the skin surface. Advances in non-invasive technologies will be required for this type of sensor.

#### ***Biological and Biomimetic Photon and Electron Transfer Materials (Technology Items K and Q in Table 3.0-2)***

Bacterial Rhodopsin is a transmembrane protein of approximately 27 kilodaltons and is light-sensitive. When exposed to yellow light, it pumps a proton from the interior of the cell-membrane to the exterior through a photocycle. During this photocycle, it passes through several intermediate states with unique characteristics and life times. This protein could be faster than a Josephson Junction for switching and could operate at room temperature. It has potential for holography, information storage and retrieval at the molecular level, and molecular computing. An artificial retina using a light-sensitive material, such as bacterial Rhodopsin or one of the porphyrin containing dyes on a chip, has been produced in prototype form. Such a device could be implanted in the eye and electrically connected to the optical nerve. Although the signals sent to the brain will not be the same as those in normal eyes, the brain can learn the meaning of the signals and, in effect, see. Using this material as an artificial eye for both human and robot application will be possible.

Phthalocyanine is a biomimetic molecule that has properties similar in some respects to bacterial Rhodopsin. It is a photosensitive porphyrin-like dye. When placed in a lipid membrane together with other compounds, it shows photo effects. As with other photosensitive materials that are reversible, it could be useful for molecular electronic applications.

#### ***Self-Assembly Systems, Data Fusion Arrays, and Characterization of the Sensor Surface (Technology Items H,O,R in Table 3.0-2)***

Most recent approaches have focused on exploiting the interaction of binding molecules with the surface of the sensor to construct sensors and provide quality control in the production of sensors. Techniques with sensitivities that can be applied to this problem include, in part, Atomic Force Microscopy (AFM), optical tweezers, membrane micropipette manipulations, and manipulation of functionalized magnetic beads by magnetic force fields. All these approaches have evolved toward methods used in analyzing molecular interactions that are most suitable for interrogating the interactions of a single molecule. AFM has been used to measure individual molecular interactions by separately modifying the surfaces of the AFM probe and the target surface with complementary binding agents. Atomic force microscopes and Near Field Scanning Optical Microscopy (NSOM) will make it possible to provide quality control for microscale and nanoscale fabrication. As an example, avidin passively adsorbed to the surface of the AFM probe was used to scan the surface that was derivatized with biotin. The rapid association of avidin with biotin was observed as the two surfaces came into closer contact and eventually touched. On retracting the AFM probe from the biotin-coated surface, the force fluctuations between the avidin and the biotin could be measured. The AFM system allows structural defects in thin films to be recognized at Angstrom-level resolution.

The speed at which the AFM probe pulls away from the substrate significantly affects the force that is needed to rupture the receptor-ligand complex. Direct measurements of the forces between complementary strands of DNA were measured by AFM, where sample DNA was bound to the AFM probe and substrate surfaces by complementary capture of oligonucleotides. For nucleic acid detection of DNA or RNA sequences in samples where these analytes are in the range of 100 to 1,000,000 copies, some form of amplification is required.

#### ***ADDITIONAL DATA***

Tables 3.2-1A and 3.2-1B present additional data on this developing critical technology.

#### ***WORLDWIDE TECHNOLOGY ASSESSMENT (See Figure 3.2-1)***

Several nations, including Canada, France, Germany, Japan, the Netherlands, Sweden, and Switzerland, the United Kingdom, and the United States, have advanced capabilities in sensor technology. Russia and Israel are also advanced in

these technologies. Much of foreign investment in biosensors is in the pharmaceutical and commercial areas. Most of the current, field-hardened detection, warning, and identification systems are for chemical agents. Several multi-array sensor systems are in development and should be available for use in mobile systems in the 5-year period. These multi-array systems will be able to detect and identify biological agents based on genomics, immunogenics, combinatorial chemistry, and proteomics. The leading edge technologies are present in Germany, France, Israel, Japan, the United Kingdom, and the United States.

**Table 3.2-1A. Biological Sensors Militarily Critical Technologies**

<b>Technology</b>	<b>Potential Developing Critical Technology Parameter</b>	<b>Rationale</b>	<b>Critical Materials</b>	<b>Technical Issues</b>	<b>Joint Vision 2010 DoD S&amp;T Plan</b>	<b>Unique Test, Production, and Inspection Equipment</b>
<i>Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Biomedical Technologies, Part III MCTL)</i>	The gene sequence codes of PAIs; determine epitopes specific for AG BW agents.	Genomic elements of biological agents determine pathogenicity; epitope can identify biological agents; multi-array sensors allow rapid unambiguous detection and identification of biological agents.	Complimentary DNA sequence or epitope/Gke surface.	Placement of complimentary gene sequences or antibodies on micron-level pmod elements in addressable manner.	Full dimensional protection.  See Table A-7.	None identified.
<i>Biosensors for odors/light/sound/pressure</i>	Chemical to electron/phonon transduction; pressure to electron/phonon transduction.  Incorporate sensor in thin film; MEMS.  Design sensor surface to accommodate attachment of molecular recognition elements ( $10^4$ per pixel) in a functionally active state.	Specific chemical or sound patterns that provide unambiguous identification of target (midterm).	Host transducing materials.	Production of sensor surface containing biomolecules in an active form; data fusion correlating known patterns with real-time threat conditions.	Full dimensional protection; precision engagement; dominant maneuver.  See Table A-7.	None identified.

**Table 3.2-1B. Biological Sensors Militarily Critical Technologies**

<b>Technology</b>	<b>Military Applications</b>	<b>Unique Software</b>	<b>Center of Technology Development: Military or Commercial</b>	<b>Commercial Applications</b>	<b>Commercial Technology Requires Development for Military Use</b>	<b>Access To Technology</b>	<b>Other Important Data</b>
<i>Multi-array sensors for detecting biological agents (bacterial, viral, fungal), genome sequences, or antigenic epitopes (see Biomedical Technologies, Part III MCTL)</i>	Multiple applications, including protecting soldiers against biological agent and disease in deployed areas.	Database of PAIs and cell surface markers.	Medical/ pharmaceutical food industries lead.	Clinical detection of infectious agents; food processing.	Biomedical and food industry lead military applications.	Ready access.	None identified.
<i>Biosensors for odors/light/sound/pressure</i>	Identifies movement of personnel, armor, and target location; stores high-density information.	Algorithm of chemical light/ sound or pattern unique to targets.	Food industry; chemical processing; military.	Food spoilage; toxicant release.	Military and food industries can have similar impact on technology.	Ready access.	None identified.

Country	Molecular Recognition Components	Biological and Biometric Photon and Electron Transfer Material	Self-Assembly Systems, Data Fusion Arrays, and Characterizations of the Sensor Surface
Australia	●●●=	●●+	●●+
Canada	●●●●=	●●●+	●●●+
China	●●=	●●+	●●●+
Cuba	●●+	●+	●+
Czech Republic	●●●=	●●=	●●●=
Egypt	●=	●=	●=
France	●●●●=	●●●●=	●●●●-
Germany	●●●●=	●●●●=	●●●●-
Hungary	●●●=	●●=	●●=
India	●●●=	●●=	●●=
Iran	●●=	●=	●=
Iraq	●=	●=	●=
Israel	●●●●-	●●●=	●●●=
Italy	●●●=	●●●=	●●●=
Japan	●●●●	●●●●=	●●●●
Malaysia	●=	●●=	●●=
Netherlands	●●●●●+	●●●●●=	●●●●●=
North Korea	●=	●=	●=
Norway	●●=	●●=	●●=
Poland	●●=	●●=	●●=
Russia	●●●-	●●●●-	●●●-
Singapore	●=	●●=	●●=
South Korea	●●●=	●●=	●●+
Sweden	●●●●●=	●●●●●=	●●●●●=
Switzerland	●●●●●=	●●●●=	●●●●●=
Syria	●=	●=	●=
Taiwan	●●=	●●●=	●●●=
Ukraine	●●=	●=	●=
United Kingdom	●●●●●=	●●●●●-	●●●●●=
United States	●●●●	●●●●	●●●●

**Legend: Capability in Technology Elements:** ●●●● Most   ●●● Many   ●● Some   ● At Least One  
**Trend Indicators: Capability relative to the United States:** "+" (Increasing), "=" (Static), "-" (Decreasing)

Figure 3.2-1. Biological Sensors Technologies Area Worldwide Capability Assessment

## SECTION 3.3 BIOMATERIALS AND NANOFABRICATION

### OVERVIEW

The rapid progress in biochemistry and molecular biology has provided industry with many new classes of materials. These include structural materials (silks and bioceramics, such as chitins); electron/photon conductive polymers, such as cytochrome and polyporphyrins; and ion gating molecules, including bioreceptors (adhesives from barnacles that can function on wet surfaces); and biocompatible lubricants. The military uses of these materials include miniaturization of electron circuits; lightweight, energy-efficient piezoelectric sensors for detection of delamination; exoskeletal supports for personnel; and camouflage/stealth. Because many biomaterials can self-assemble, these materials have been used to pattern sensor surfaces having thicknesses in the nanometer range. The biomaterials are produced in living organisms. The cost of production is modest, requiring only fermentation-like facilities. Because the living cells replicate, small starter cultures can be used to produce large numbers of organisms. The living organisms require aqueous systems for growth and, therefore, are environmentally advantageous. Organic solvent requirements are minimized, thereby reducing remediation, treatment, and pollution costs. The technology of genetic engineering permits proteins synthesized in one order or species of animal to be synthesized in other organisms. By this method, proteins normally made only in mammals, including humans, can be produced on a large scale in bacteria, yeast, or plants. One form of such engineering involves the use of cassette mutation, most studied in yeast. Cassette mutation allows entire genes of interest to be inserted into a microorganism for large-scale manufacture of the gene product.

The following subareas are critical to increased military superiority and advanced economic competitiveness:

- **Biomaterials.** Production of high-tensile-strength, low-weight materials.
- **Nanofabrication.** Fabrication of miniaturized electronic and photonic switches, circuits, and molecular motors

### RATIONALE

Biopolymer-based systems have specificity and selectivity with regard to the chemical processes they facilitate. A major advantage of biosystems is their self-assembly properties. Such self-assembly occurs at the nanometer scale. The materials provide opportunities in the manufacture of artificial retinas, microsensor chips,

#### *Highlights*

- Miniaturization at the nanometer-scale level will facilitate high-density information storage, retrieval, and processing.
- Biomaterial-based circuit and switching devices will be available on the nanometer scale to enable rapid and accurate responses to changing requirements for applications of military force.
- Biopolymer-based artificial retinas have the potential to advance night vision, missile guidance, and reconnaissance systems.

and electron/phonon switching devices. These technologies provide large numbers of chips and electron/phonon switching devices. These technologies provide large numbers of lightweight sensors that operate in ambient temperatures. Military applications include protective clothing, stealth coatings, missile guidance systems, and underwater acoustic sensors. Production and maintenance quality control at the molecular level have profound implications for reliable operation of military systems in high-stress environments.

### TECHNOLOGY DESCRIPTIONS

#### *Biomaterials (Technology Items K and Q in Table 3.0-2)*

Within a decade, scalable, artificial imagers with optical response functions that more closely resemble human retinal response will be developed. These artificial imagers will be scalable to large sizes, will be low cost, and will have on-chip image processing functions. The materials include amorphous Silicon (a-Si) thin-film transistor (TFT) imaging arrays in conjunction with photosensitive layers comprised of materials such as bacteriorhodopsin (bR). Bacteriorhodopsin has the unique attribute that the generated photo response of a bR film yields the integral characteristic of the incident optical image. This means that the bR layer generates a photovoltage whose magnitude is proportional to the time rate of change of the incident optical signal. Thus, an imaging system with bR as the photosensitive layer performs optical processing functions that lead to systems that respond as edge or motion detectors. Combined with more conventional imager response functions, these bR-based imagers can yield a better picture of remote battlefield conditions. In addition,

fabricating imagers with pixels that use the orientation properties of bR films is possible. By fabricating individual pixels with regions that exhibit opposite orientation, generating optical response functions that closely mimic the response of retinal ganglion cells is possible. Such cells have particular sensitivity to moving or stationary target tracking. These are required elements of smart targeting weapons. These imagers could replace traditional sensor elements for strike, night vision, or reconnaissance missions.

Lightweight, chemical-resistant, shrapnel-resistant, self-cooling materials are under development, using biological systems as models. The ceramic coatings of insects and shellfish are metal-protein-carbohydrate complexes. Spider silk, plant tassel silk, and silkworm silk all have high strength-to-mass ratios. These materials may be readily modified because proteins and carbohydrates contain many functional groups for grafting other materials. This ease of grafting has advantages in attachment of sensors to the clothing fabric.

Signature reduction of a soldier may be achieved using a uniform made from a polymer material with side chains of a chiral material that reduces his signature to radar. A material that will reduce the infrared (IR) signature of a soldier at night is also very likely within the next 5 to 10 years—if it is not already available.

#### ***Nanofabrication (Technology Items H,O,R in Table 3.0-2)***

Biomaterials, such as proteins, lipids, and nucleic acids, can self-assemble. Self-assembly is the formation of organized, patterned structures without external direction. The fidelity of the self-assembly is extraordinarily high. These self-assembled components can be complex and perform unique functions. An example of self-assembly is the formation of pores by the addition of hemolysin from *Staph. aureus* to a solution containing lipid membranes. Without any external manipulation, the proteins will join together and form a pore in the membrane. Other examples include the appropriate folding of proteins as they are synthesized from messenger RNA and the assembly of a biomolecular motor that consists entirely of proteins (dynein and kinesin) combined in such a fashion that the product is an engine. Many polymers can self-assemble into membrane-like structures. Examples are the formation of monolayer of alkylthiols on gold surfaces, silanes on glass and metal oxides, and organic molecules into polymers on conducting surfaces by electropolymerization.

Within the next 5 to 15 years, using self-assembling techniques to produce nano-size gears, motors, and other mechanical and electronic components in the nanometer size range will be possible. Such devices will find application in monitoring human health, behavior, and the environment. They may even be capable of assembling within the body by simple addition in “monomeric form.” These devices will perform functions presently requiring complex, expensive, and proportionally large integrated circuitry. They can also perform tasks not related to humans.

Using Microelectromechanical Systems (MEMS) technology and possibly self-assembly and nanofabrication, it will be possible to produce small devices capable of switching. These devices may be used to change wavelength in optical systems, turn electronic devices or circuits on and off, or monitor specific phenomenon in military systems, the environment, or the human body. The ability to change wavelength can lead to low-weight iconographic presentation formats on helmet mounted displays (HMDs).

Atomic Force Microscopy (AFM) and Near Field Scanning Optical Microscopy (NSOM) use a technique that involves maintaining close contact between a cantilevered probe and a surface by maintaining either constant potential, resistance or other measurable quality. The device produces a “picture” of surfaces at the molecular level. This picture can be the physical surface, the electrical potential, the resistance, the magnetic differences, or several other qualities that this surface may possess. In all these cases, the device produces a diagram of that surface or that surface property at the molecular level.

In the next decade, the devices will be available in a hardened and portable form. With portable devices, examining surfaces in our external environment for changes, contaminants, or other characteristics that may have commercial or military application will be possible. One possible example of a commercial application would be the production of silicon or diamond chips for integrated circuits. Using atomic force microscopes and NSOM, the quality control of microscale and nanoscale fabrication can be realized. Such a device on a production line would be useful in looking for defects if it could be designed to scan surfaces at a relatively rapid rate.

#### ***ADDITIONAL DATA***

Tables 3.3-1A and 3.3-1B present additional data on this developing critical technology.

#### ***WORLDWIDE TECHNOLOGY ASSESSMENT (See Figure 3.3-1)***

Technologically advanced nations have recognized the civilian and the military opportunities provided in biomaterials. France, Germany, Japan, the Netherlands, Sweden, Switzerland, the United Kingdom, and the United States are overall world leaders in this area. Other nations, including Israel, also conduct leading-edge research and development (R&D). Russia had a leading edge in the development of artificial retinas, but this advantage has diminished in recent years. In Germany, Japan, and the United States, the chemical industry has been a dominant driver of advances in biomaterials and bioelectronics.

**Table 3.3-1A. Biomaterials and Nanofabrication Militarily Critical Technologies**

Technology	Potential Developing Critical Technology Parameter	Rationale	Critical Materials	Technical Issues	Joint Vision 2010 DoD S&T Plan	Unique Test, Production, and Inspection Equipment
<i>Smart biomaterials</i>	Optimizes match or contrast color of cloth to environment (e.g., electroactive polymers, bioceramics, HMD); indicates condition of structure by changing color.	Biopolymers can change wavelength absorbed and emitted or change function as piezoelectrically active materials.	None identified.	Develop biopolymers that have tunable absorbing/emitting properties in the IR, visible and UV range (800- to 260-nm wavelength); embed piezoelectrically active biopolymers in matrix while retaining structural integrity (midterm).	Dominant maneuver; full dimensional protection; full spectral dominance.  See Table A-7.	None identified.
<i>Self assembly biomaterials</i>	Produces nanometer-scale materials (midterm).	Biopolymers self assemble and can form contractile, vectorially oriented filaments, which allow for production of nanometer-scale motors, transducers, and guidance systems.	Contractile proteins that self assemble.	Insertion of contractile proteins into stable lipid-fluid monotypes with vector movement control.	Dominant maneuver; full dimensional protection; full spectral dominance.  See Table A-7.	None identified.

**Table 3.3-1B. Biomaterials and Nanofabrication Militarily Critical Technologies**

Technology	Military Applications	Unique Software	Center of Technology Development: Military or Commercial	Commercial Applications	Commercial Technology Requires Development for Military Use	Access To Technology	Other Important Data
<i>Smart biomaterials</i>	Uses in camouflage; determines structural integrity of aircraft.	Algorithm for matching tuned materials to environment.	Primarily military.	Structural integrity of materials that become deformed.	None identified.	Limited.	None identified.
<i>Self assembly biomaterials</i>	Micromotors for guidance systems.	None identified.	Medicine; manufacturing.	Nanometer-scale motors; microfluidics.	None identified.	Ready access.	None identified.

Country	Biomaterials	Nanofabrication
Australia	●●	●●
Canada	●●●	●●●
China	●●	●●
Cuba	●●	●
Czech Republic	●●	●●
Egypt	●	●
France	●●●●	●●●●
Germany	●●●●	●●●●
Hungary	●●	●
India	●●	●●
Iran	●	●
Iraq	●	●
Israel	●●●	●●●
Italy	●●●	●●
Japan	●●●●	●●●●
Malaysia	●●	●
Netherlands	●●●●	●●●●
North Korea	●	●
Norway	●●	●●
Poland	●●	●●
Russia	●●●	●●●
Singapore	●●	●●
South Korea	●●	●●
Sweden	●●●●	●●●●
Switzerland	●●●●	●●●●
Syria	●	●
Taiwan	●●●	●●
Ukraine	●	●
United Kingdom	●●●●	●●●●
United States	●●●●	●●●●

Legend: Capability in Technology Elements: ●●●● Most ●●● Many ●● Some ● At Least One

Figure 3.3-1. Biomaterials and Nanofabrication Technologies Area Worldwide Capability Assessment

## SECTION 3.4 INDIVIDUAL AND GROUP PROTECTION

### OVERVIEW

Technological developments in novel materials, containment capability, and telecommunications have improved survivability and effectiveness of military forces. New insights regarding the molecular mechanisms involved in pathogenicity have given rise to countermeasures that can be employed if people are exposed to infectious diseases or agents. During the next two decades, novel material developments will provide filters that bind and inactivate biological agents, with minimal reduction of air flow, thereby protecting soldiers in the field or in contained vehicles. Telecommunications and the development of haptic devices are key to the introduction of remote surgical procedures that medical corpsmen can perform under the guidance of surgeons located at a distance from the battle arena. These methods of telemedicine have applications in training physicians and in delivering medicine to people residing in less densely populated areas. This innovation is important because early effective treatment of trauma provides higher survival rates and because injury of forces requires extensive deployment of support forces. It is also important because the military forces are being downsized and because physicians are more frequently deployed in sites distant from battle. The Biomedical Science section of Part III of the Militarily Critical Technologies List (MCTL) has an extensive consideration of telemedicine.

Biotechnology advances have also provided insights into the molecular basis of immune protection, vascular fluid loss, and neural regeneration. Enhanced immune competency permits forces to function at maximal strength after deployment. Sick calls are normally a problem during the first few weeks after deployment. Enhancement of the immune response by vaccination with super-antigens, by treatment with biological response modifiers (BRMs), or by food additives may ameliorate the problem. Extensive fluid loss is a primary cause of loss of life from traumatic injury. Applications of newly developed compatible blood clotting biopolymers, administered intra-abdominally to stanch blood loss, will help to ensure the survivability of ground forces. Spinal cord injuries constitute a major cause of long-term disability because current techniques do not permit regeneration of severed Central Nervous System (CNS) connections. New techniques, using growth factors and biocompatible guidance materials, are being developed to facilitate regrowth and repair of the CNS.

The following subareas are critical to increasing individual and group protection and survivability:

- Biomedical imaging and transporting pods

### *Highlights*

- Novel biomaterials will enable reinsertion of military persons into active service at a rate several times faster than current techniques.
- Performance indicators will enable timely and appropriate intervention and maintain readiness and fitness assessment.
- Pharmaceuticals and performance enhancers will protect the combat force from endemic disease and extend mission performance capability.
- Biological tests will decrease combat morbidity and mortality by a factor several times faster than existing techniques.
- Prompt protection of human systems through analysis and assessment of food, water, and environmental factors will reduce the occurrence of disabling human disease and increase capability in a fighting force with fewer combatants.

- Encapsulation
- Pathogen Genome Project and pathogenicity islands (PAIs)
- Blood substitutes and biocompatible clotting matrices
- Remote locator of persons to permit rescue of captured personnel
- Water purification
- Biomarkers for toxicant/stress exposure.

Enhanced resistance of people to disease organisms (biological agents and endemic organisms) before and after deployment/exposure to impact trauma and to burn injury and the subsequent reduction in sick calls are goals to be achieved by the newly emerging biotechnologies and medical advances. The Biomedical Science section of Part III of the MCTL discusses the role of environmental toxicants on performance and the protection of people from such toxicants.

Enhanced prophylaxis can be achieved by using active vaccination against biological agents or infectious agents endemic in deployed areas. Vaccination with super-antigens or advanced adjuvants (i.e., improved antigen presentation) can upregulate the immune system before deployment and provide protection in a 4-day period rather than the usual 10-day post-vaccination period. The enabling technologies include genomic sequencing of all known threat agents and infectious disease organisms; multi-component, multi-valent vaccination systems to upregulate the immune system; and the development of immune response modifiers, including

interferons and interleukins, having the potential to enhance immune response under crisis situations. The sequencing of PAIs can reduce the total number of vaccines needed.

New technologies that protect people before deployment include DNA vaccines. These vaccines have become available as an additional technology to the current vaccine systems that have eliminated small pox and controlled childhood diseases.

Recent advances have been realized in technology and molecular biology to treat personnel in the 12- to 72-hour period after exposure to B agents. Some of these advances followed research on the treatment of AIDS. People can be protected from the clinical signs of viral infection after exposure to agents because the virus in the lung or intestinal system must attack cells at secondary sites, such as the kidney, nervous system, blood cell, or other organ system. For the virus to attack successfully, it must enter the cell and must often travel to the nucleus. Then, the newly synthesized nucleic acid must be coated by the protein capsid. Cysteine protease inhibitors can block entry of the virus to cells, inhibitors of cytoplasmic nuclear transport can inhibit the second step, and inhibitors of molecular chaperones can inhibit the nucleic acid-viral protein coat interaction.

New sets of antibiotics that inactivate PAIs may have utility in individual and group protection. These antibiotics can be anti-sense materials or chemicals similar to traditional antibiotics. Developing antibiotics that have not been used to eliminate the development of drug resistance in the general population is important.

## **RATIONALE**

A defensive capability against biological threat agents provides a nation with the technology to continue operations in a contaminated environment, thereby diminishing the likelihood that such agents will compromise a well-protected military force. New understandings of the human organism have led to the development of pharmaceuticals that sustain human performance. Information about the human genome also provides a new capability to determine peoples' susceptibility to naturally occurring toxicants and infectious agents. Biotechnology has the capability to fashion materials that bind toxicants with a high affinity and, thereby, inactivate such material. An awareness of the peoples' predisposition to environmental toxicants and of the nature of materials that bind such chemicals will allow military capability to be maintained in a symmetric manner and provide maximum deterrence. These technologies have broad applications in the civilian chemical industry, hazardous industrial operations, and the detection of contraband. The interface of medicine and space satellite communication has given rise to a new field: telemedicine. This new area will markedly improve the surgical care provided to those in the military who experience traumatic injury, blood loss, and shock. It will permit placement of support physicians at a distance from the front line of combat while providing continuous visual, auditory, and haptic input to medics in the field.

## **TECHNOLOGY DESCRIPTIONS**

### ***Biological Imaging and Transporting Pods (Technology Item J in Table 3.0-2)***

Pod-like units that permit patients who have been exposed to biological agents to be transferred to remote sites have been built. This protects troop cohorts from infection. The pods have a controlled environment, can be incorporated into a battle dress uniform (BDU), are lightweight, and can be decontaminated and reused. The pod contains a dosimeter of chemical and biological agent exposure (similar to a film badge for radiation).

The pod is a bi-directional system that reports the personal information and also receives information about the environment, allowing the individual to take the appropriate action. This does not necessarily require individual-level monitoring if the device can be electronically linked to a nearby area monitor or sensor. The pod can encapsulate a patient in a small, automated decontamination (DECON) pod that can be managed by a crew smaller than that needed to encapsulate a large DECON team.

### ***Encapsulation (Technology Item L in Table 3.0-2)***

Many biologically active materials lose activity when exposed to oxidizing environments or to dilution in aqueous environments. Encapsulation of the biologically active material in a variety of matrices (e.g., liposomes, lactides, hydrogels) stabilizes the biomaterials and can provide a delivery vehicle for slow release. The slow release can be activated by enzymes normally found in the body or by pulsed electromagnetic signals. The release is a function of the chemical nature of the encapsulating material. Encapsulation can also provide targeted delivery of the biologically active material to specific organs if the capsules are coated with antibodies, lectins, or polycations. Encapsulation technology has potential applications in delivering taggants for a variety of military applications.

### ***Pathogen Genome Project and Pathogenicity Islands (PAIs) (Technology Item N in Table 3.0-2)***

The entire genome of many pathogenic organisms and of identified biological agents has been determined. As a result, the genomic sequences responsible for increased virulence and PAIs of these organisms have been characterized. It is apparent that the number of PAIs is smaller than the number of biological agents because the same PAIs are shared by several organisms. This observation can lead to the development of new antibiotics and anti-sense technologies to reduce virulence.

***Blood Substitutes and Biocompatible Clotting Matrices (Technology Item S in Table 3.0-2)***

Polymers having oxygen-carrying capabilities are available. Many of these are fluorinated compounds but have a disadvantage of showing hepatotoxicity. Biopolymeric oxygen-carrying compounds and clot-inducing compounds are being developed with anticipated product availability in the 2005 time period. These new products should have universal acceptor compatibility and should not require human donors.

***Remote Locator of Persons To Permit Rescue of Captured Personnel (Technology Item T in Table 3.0-2)***

Compounds may be developed that, when metabolized, will result in the excretion of compounds that are strong chromophores. Operators must be able to turn on or off for covert missions. The signal generator can be placed internally so it cannot “easily” be removed by the enemy for counter use. The device will be low cost and contain a physiological “honesty” checker so if “scared” Johnny cuts his finger, he will not activate this device unnecessarily and draw needed assets. The system may be used to locate a sailor overboard.

***Water Purification (Technology Item U in Table 3.0-2)***

Current technology requires use of reverse osmosis (RO). Desalinization of sea water and purification of contaminated water can be achieved using a combination of filtration and RO. New technologies that are effective in defouling and regenerating the capillary tubes in the RO system are being developed.

Transgenic flora and fauna are being developed to produce renewable resources (water, food, therapeutics). Microbes capable of bioremediation and terraforming terrain to shape the environment are being examined.

***Biomarkers for Toxicant/Stress Exposure (Technology Items M,P,V in Table 3.0-2)***

Humans and other animals synthesize a variety of biological compounds when challenged with fever, infection, or emotional stress. The synthesized compounds may be of low molecular weight (e.g., adrenalin) or high molecular weight (e.g., acute phase proteins, glutathione transferases, cytochrome P 450). Exposure of individuals to stress, exhaustion, or other adverse conditions also results in changes in electrophysiological and behavioral characteristics of the affected people. The changes in the profiles of body chemicals, electrophysiological patterns, and behavior may be used as signatures to evaluate fitness and readiness.

***ADDITIONAL DATA***

Tables 3.4-1A and 3.4-1B present additional data on this developing critical technology.

***WORLDWIDE TECHNOLOGY ASSESSMENT (WTA) (See Figure 3.4-1)***

Nations with advanced capability in individual and group protection include France, Germany, Israel, the Netherlands, Sweden, Switzerland, the United Kingdom, and the United States. Other nations have advanced technologies in pharmaceuticals or biopolymer grafting onto fibers. This area also requires leading-edge communications and space satellite industries for the telemedicine component. France, Japan, Russia, the United Kingdom, and the United States have strength in this area although the economic realities in Russia have diminished their strength. China is rapidly increasing capability in the space satellite area and, as a consequence, will have capability in telemedicine. Many leaders in these technologies are multi-national (e.g., Celanese, Hoechst, Dupont), and the rapid advances are not nation specific.

**Table 3.4-1A. Individual and Group Protection Militarily Critical Technologies**

<b>Technology</b>	<b>Potential Developing Critical Technology Parameter</b>	<b>Rationale</b>	<b>Critical Materials</b>	<b>Technical Issues</b>	<b>Joint Vision 2010 DoD S&amp;T Plan</b>	<b>Unique Test, Production, and Inspection Equipment</b>
<i>Encapsulation</i>	Releases chemical or biological response modifiers on demand (near term).	Biologically active materials, such as vaccines, antitoxins and performance sustainers, can be encapsulated, inserted in soldier, and released on demand.	Encapsulation vehicles that stabilize biochemicals and release high percentage of active biological (greater than 80 percent).	Develop matrices that bind biological materials to delay release.	Full dimensional protection.	None identified.
<i>Novel antivirals and antibiotics (see Biomedicine section, Part III MCTL)</i>	Intervenes in infectious entry into target and infection of secondary organ systems; replicates in cells and releases infectious particles (near term to midterm).	Antivirals and novel antibiotics can protect person exposed to infectious agents from clinical signs of disease.	Antivirals and novel antibiotics.	Inhibit viral uptake; intracellular transport and maturation; create new antibacterials and reduce development of antibiotic resistance.	Full dimensional protection.	None identified.
<i>Organ culture; tissue growth (see Biomedicine section, Part III MCTL)</i>	Replaces organs (midterm).	Traumatic injury results in long-term damage to internal organs and neural function. Replacing heart valves and bridging of transected spinal cord can lead to restored function.	Production of organ stem cells and organs that are accepted in immune-competent people.	Grow organs that will not be subjected to tissue rejection; grow organs in large enough mass to assume function of destroyed abdominal organs.	Full dimensional protection.	None identified.
<i>Temperature and biotic system controlled transport pods</i>	Develops pod that can stanch bleedings, have sterile environment, and contain B agents (midterm).	Protect troop cohort from B-agent-contaminated individuals.	Materials suitable for filtration, body covering, weight bearing, shock absorbing, and humidity control.	Maximize survivability of exposed/wounded soldier while eliminating exposure of cohort.	Full dimensional protection.	None identified.

**Table 3.4-1B. Individual and Group Protection Militarily Critical Technologies**

<b>Technology</b>	<b>Military Applications</b>	<b>Unique Software</b>	<b>Center of Technology Development: Military or Commercial</b>	<b>Commercial Applications</b>	<b>Commercial Technology Requires Development for Military Use</b>	<b>Access To Technology</b>	<b>Other Important Data</b>
<i>Encapsulation</i>	Provides protection against B agent; SUSOPS; sustains performance.	None identified.	Biomedical, pharmaceutical; cosmetics; drug delivery.	Biomedical, pharmaceutical; cosmetics; drug delivery.	Drug delivery; vaccination.	Ready access.	None identified.
<i>Novel antivirals and antibiotics (see Biomedicine section, Part III MCTL)</i>	Protects soldier from infectious agents.	None identified.	Biomedical and pharmaceutical industry and food industry.	Biomedical and pharmaceutical industry and food industry.	Health, food quality.	Ready access.	None identified.
<i>Organ culture; tissue growth (see Biomedicine section, Part III MCTL)</i>	Stanches abdominal bleeding; repairs injuries to spinal cord, brainstem, and brain.	None identified.	Health care dominates.	Health care; pharmaceutical production.	Medical organ replacement.	Ready access.	None identified.
<i>Temperature and biotic system controlled transport pods</i>	Allows reinsertion of soldier; protects group.	Vital sign monitor.	Primarily military; emergency preparedness teams in isolated locations.	Biomedical.	Rural medical emergencies and preparedness tasks.	Ready access.	None identified.

Country	Individual Protection (Encapsulation, PAIs, Blood Substitutes, Biomarkers)	Group Protection (Biological Imaging and Transporting Pods, Remote Locator, Water Purification)
Australia	●●	●●
Canada	●●●	●●●
China	●●	●
Cuba	●●	●
Czech Republic	●●●	●●
Egypt	●	●
France	●●●●	●●●
Germany	●●●●	●●●
Hungary	●●	●
India	●●	●
Iran	●	●
Iraq	●	●
Israel	●●●	●●●●
Italy	●●	●●
Japan	●●●	●●●
Malaysia	●	●
Netherlands	●●●●	●●●●
North Korea	●	●
Norway	●●	●●
Poland	●●	●
Russia	●●●	●●●
Singapore	●●	●
South Korea	●●	●
Sweden	●●●●	●●●
Switzerland	●●●●	●●●●
Syria	●	●
Taiwan	●●	●
Ukraine	●●	●
United Kingdom	●●●●	●●●●
United States	●●●●	●●●●

Legend: Capability in Technology Elements: ●●●● Most ●●● Many ●● Some ● At Least One

Figure 3.4-1. Individual and Group Protection Technologies Area Worldwide Capability Assessment

## **APPENDIX A.**

### **MILITARY NEEDS MET BY BIOLOGICAL TECHNOLOGIES**

#### ***INTRODUCTION***

Appendix A tracks the applications of developing biotechnologies to known and documented military needs. This kind of cross reference is made more challenging because of changes in program funding and by differences in nomenclature and format among the Services. Accordingly, Table A-1 presents an aggregation keyed to the biotechnology areas defined in Table 3.0-1. Tables A-2 and A-3 address Army needs, Tables A-4 and A-5 address Navy needs, and Table A-6 addresses Air Force needs. Table A-7 is organized by functional biotechnology application and indicates Service interest by program for the three military components.

## APPENDIX A.

### MILITARY NEEDS MET BY BIOLOGICAL TECHNOLOGIES

**Table A-1. Military Needs Met by Developing Biotechnologies**

Item Number	Biotechnology Area <sup>1</sup>	Item Number	Biotechnology Area <sup>1</sup>	Item Number	Biotechnology Area <sup>1</sup>
1. Personal protective system	K	13. Info pre-processing/data fusion and information display	C	25. Host responsive modulation	C,E,G
2. Multi-component, multi-valent vaccination system	P	14. Metabolic sensors	I	26. Psychological maintenance and augmentation	A,B,C,D,E,V
3. Substitute blood	S	15. Real-time disease and injury surveillance	F,I,V	27. Small MRI system	F
4. Real-time, integrated alert/detection and identification system	I,V	16. Analgesia without CNS depression	G	28. Minimize physiological effects of injury	F,S,T
5. Integrate medical into C2 architecture	J	17. Collective protective system	I,K,M,P,T	29. Advanced screening/profiling	A,B,C,D,E,G,M
6. Enhanced prophylaxis and therapeutic agents	P,V	18. Detect/alert/ID systems (required to link into the Medical Planning System)	I,J,T	30. Distributed decision-making	C,D,E,G
7. Distributed medicine	J,V	19. Real-time training	A,B,C,D,E,F,G	31. Readiness tracker	E,F,V
8. Performance enhancing drugs/diet/equipment	A,B,C,G,V	20. Locator	I,T	32. Add-on to PSM for status of forward-deployed personnel	I
9. Laser defensive system	K	21. Rapid field diagnostics (dipstick for malaria)	I	33. Spatial re-orienter	C,E
10. Non-invasive diagnostics	F,I,J,N	22. Individual self-decontamination	I,K,L	34. Recyclable decontamination agent	I,J,K,L
11. Safe water supply	U	23. Personnel decontamination, isolation, and evacuation	I,K,L,P	35. Biodosimetry capability to assess/permit medical triage	I,J,V
12. Enhanced physical/psychological training	G	24. Blood clotting material/wound repair	S	36. Power/fuel cells	H,K

**Note 1 for Table A-1:** *The information in this column is taken from Table 3.0-1.*

**Table A-2. Developing Biotechnologies and U.S. Army Requirements**

<b>Military Needs <sup>1</sup></b>	<b>USA TRADOC Code <sup>2</sup></b>	<b>Military Needs <sup>1</sup></b>	<b>USA TRADOC Code <sup>2</sup></b>	<b>Military Needs <sup>1</sup></b>	<b>USA TRADOC Code <sup>2</sup></b>
1. Personal protective system	MTD11	13. Info pre-processing/data fusion and information display	–	25. Host responsive modulation	–
2. Multi-component, multi-valent vaccination system	CSS06	14. Metabolic sensors	CSS05, CSS13, CSS14	26. Psychological maintenance and augmentation	CSS14
3. Substitute blood	CSS11	15. Real-time disease and injury surveillance	CSS07, CSS08, CSS09	27. Small MRI system	CSS07
4. Real-time, integrated alert/detection and identification system	MTD19	16. Analgesia without CNS depression	CSS08	28. Minimize physiological effects of injury	CSS07
5. Integrate medical into C2 architecture	CSS05	17. Collective protective system	EEL08	29. Advanced screening/profiling	BC23, TRD02
6. Enhanced prophylaxis and therapeutic agents	CSS06, CSS13	18. Detect/alert/ID systems (required to link into the Medical Planning System)	CSS05	30. Distributed decision-making	CSS05
7. Distributed medicine	CSS05	19. Real-time training	CSS24, DBS26, MDT17	31. Readiness tracker	CSS05
8. Performance enhancing drugs/diet/equipment	CSS14	20. Locator	DSA07	32. Add-on to PSM for status of forward-deployed personnel	MTD13
9. Laser defensive system	–	21. Rapid field diagnostics (dipstick for malaria)	CSS07, CSS13	33. Spatial re-orienter	–
10. Non-invasive diagnostics	CSS07	22. Individual self-decontamination	MTD13	34. Recyclable decontamination agent	MTD13
11. Safe water supply	–	23. Personnel decontamination, isolation, and evacuation	MTD13	35. Biodosimetry capability to assess/permit medical triage	CSS05, CSS13
12. Enhanced physical/psychological training	CSS24, DBS26, TRD02	24. Blood clotting material/wound repair	CSS08	36. Power/fuel cells	CSS19, MTD06

**Note 1 for Table A-2:** See Table A-1.

**Note 2 for Table A-2:** See Table A-3

**Table A-3. Relation of U.S. Army TRADOC Code to Operational Requirements**

USA TRADOC Code	Operational Capability Requirements
BC23	Commander and battlestaff training
CSS05	Medical C4I
CSS06	Preventive medicine
CSS07	Treatment of battlefield wounds and disease
CSS08	Far-forward surgical support
CSS09	Battlefield hospitalization
CSS11	Combat health logistics system and blood management
CSS13	Provision of combat support in CB environment
CSS14	Combat stress control
CSS19	Power source and accessories
CSS24	Training support
DBS18	Near-real-time data fusion
DBS26	Training and leader development
DSA07	Real-time, on-board, all-weather precision terrain locator
DSA16	Artificial intelligence and decision aids
EEL08	Soldier/equipment protection
MTD06	Power generation
MTD11	Individual protective equipment
MTD13	NBC DECON
MTD17	Battle planning and rehearsal
MTD19	Sensors for mounted forces
TRD02	Train leadership skills

**Table A-4. Navy S&T Requirements Guidance, Department of the Navy, CNO N091  
Prepared by N911, July 1987**

Military Needs <sup>1</sup>	Naval Code <sup>2</sup>	Military Needs <sup>1</sup>	Naval Code <sup>2</sup>	Military Needs <sup>1</sup>	Naval Code <sup>2</sup>
1. Personal protective system	–	13. Info pre-processing/data fusion and information display	–	25. Host responsive modulation	–
2. Multi-component, multi-valent vaccination system	4	14. Metabolic sensors	4	26. Psychological maintenance and augmentation	–
3. Substitute blood	5	15. Real-time disease and injury surveillance	3,4	27. Small MRI system	2
4. Real-time, integrated alert/detection and identification system	–	16. Analgesia without CNS depression	3	28. Minimize physiological effects of injury	–
5. Integrate medical into C2 architecture	2	17. Collective protective system	–	29. Advanced screening/profiling	–
6. Enhanced prophylaxis and therapeutic agents	3,5	18. Detect/alert/ID systems (required to link into the Medical Planning System)	2	30. Distributed decision-making	–
7. Distributed medicine	–	19. Real-time training	–	31. Readiness tracker	–
8. Performance enhancing drugs/diet/equipment	–	20. Locator	–	32. Add-on to PSM for status of forward-deployed personnel	–
9. Laser defensive system	–	21. Rapid field diagnostics (dipstick for malaria)	2	33. Spatial re-orienter	1
10. Non-invasive diagnostics	1	22. Individual self-decontamination	–	34. Recyclable decontamination agent	–
11. Safe water supply	2,5	23. Personnel decontamination, isolation, and evacuation	–	35. Biodosimetry capability to assess/permit medical triage	2
12. Enhanced physical/psychological training	–	24. Blood clotting material/wound repair	1	36. Power/fuel cells	–

**Note 1 for Table A-4:** See Table A-1.

**Note 2 for Table A-4:** See Table A-5.

**Table A-5. Relation of Navy Code to Operational Requirements**

<b>Navy Code</b>	<b>Operational Capability Requirements</b>
1	Combat Casualty Care – Casualty Management
2	Operational Medicine – Assessment and Detection
3	Combat Casualty Care – Delivery and Treatment
4	Operational Medicine – Prevention
5	Operational Medicine – Treatment

**Table A-6. Military Needs/USAF R&D Programs Correlation Matrix**

Military Needs <sup>1</sup>	Relevant USAF Program
1. Personal protective system	[H] 1.A.01 High Altitude Protection Concepts [H] 1.A.01 Altitude DCS Prediction Model [H] 1.A.01 Advanced Life-Support Equipment [H] 1.A.04 Task Performance at High G [H] 1.A.04 Cognitive Limitations High G [H] 1.A.04 Pitch & Yaw Axis Agile Flight [H] 1.A.07.b Scientific Visualization for Research and Design [H] 1.A.07.b Accommodation Technology [H] 1.B.02 Advanced Fighter Program Life Support [H] 1.B.03.a Personal Protection in Hazardous Environments [H] 1.B.03.a SHARP EDGE [H] 1.C.01 Active and Enhanced Noise Reduction
2. Multi-component, multi-valent vaccination system	–
3. Substitute blood	–
4. Real-time, integrated alert/detection and identification system	1.C.01 Biologically Based Speaker Identification
5. Integrate medical into C2 architecture	[H] 1.B.02 Aeromedical Information Highway
6. Enhanced prophylaxis and therapeutic agents	[H] 1.A.04 Drug Effects at High G
7. Distributed medicine	[H] 1.C.03 Teleoperator Aids [H] 2.A.01 (1 of 2) Distributed Team Performance Testbed
8. Performance enhancing drugs/diet/equipment	[H] 1.A.04 High ADA Flight and Human Performance [H] 1.A.04 Helmet-Mounted Systems in High G Environment [H] 1.A.07.a Interoperable Human Model [H] 1.A.08 Comfort & Performance Under Vibration [H] 1.B.03.a Effects of Drugs on +Gz Tolerance [H] 1.C.04.b Alternative Control Development [H] 1.C.05.a Airborne Helmet-Mounted Display Oculometer [H] 1.C.05.b COMBAT EYE [H] 3.A.2 (4 of 4) Photorefractive Keratectomy [H] 3.A.3 Aerospace Neuropsychiatric Performance Enhancement [H] 3.B.1 (1 of 3) Aircrew Spectacle Frame/Lens Material Program
9. Laser defensive system	[H] 4.b.02.A Optical Radiation, Personnel Susceptibility [H] 4.b.02.A Optical Radiation, Safety Standards and Risk Assessment [H] 4.b.02.B Laser Eye Protection
10. Non-invasive diagnostics	[H] 3.B.1 (3 of 3) (Gamma Camera) [H] 3.B.1 (3 of 3) (Retinal Oximetry)
11. Safe water supply	[H] 5.a.01 Aerobic Bioremediation of a Contaminated Aquifer [H] 5.a.04 New Technologies for Oil/Water Emulsion Treatment

**Table A-6. Military Needs/USAF R&D Programs Correlation Matrix (Continued)**

Military Needs <sup>1</sup>	Relevant USAF Program
12. Enhanced physical/psychological training	[H] 1.B.03.a Strength Conditioning and +Gz Training [H] 1.B.03.a Simulation/Flying Tradeoff Study [H] 2.A.01 (1 of 2) Automated Cognitive Task Analysis [H] 2.A.01 (1 of 2) Models of Cognition Under Stress [H] 2.A.02 (1 of 3) Integrated Performance Assessment System [H] 2.A.02 (2 of 3) Training Analysis and Integration technologies for Readiness and Contingency Support [H] 2.A.03 (1 of 2) Virtual Interactive Software Technology Advancement [H] 2.A.03 (1 of 2) Virtual Interactive Instruction Development Support [H] 2.A.03 (1 of 2) Cognitive Hyperspace for Applied Engineering of Long Distance Learning [H] 2.A.03 (1 of 2) Advanced Virtual Agents for Team Training and Aiding in Remote Settings [H] 2.A.03 (1 of 2) Automated Task Analysis for Team Skill and Knowledge [H] 2.A.03 (2 of 2) Fundamental Skills Tutors [H] 2.A.03 (2 of 2) Knowledge-Based Objects for Tutoring Systems [H] 2.B.01 (1 of 3) Visual Displays Research [H] 2.B.01 (1 of 3) Eye Position Feedback for Aircrew Training [H] 2.B.03 (1 of 2) NVG Perceptual Effects Training [H] 3.A.4 Enhanced Vestibular Screening and Diagnostic System [H] 3.B.2 Health Assessment and Performance Enhancement [H] 3.B.2 Exercise Countermeasures for Fluid Homeostasis
13. Info pre-processing/data fusion and information display	[H] 1.A.02.a Crew Systems for Information Warfare [H] 1.A.02.a Crew-Centered Aiding [H] 1.A.05 Aerospace Performance Models, Simulation & Research System [H] 1.C.01 3-D Audio for Command and Control [H] 1.C.01 Advanced Communication Enhancement Technology [H] 1.C.02 Helmet-Mounted Sensory Technologies [H] 1.C.03 Haptic Stick Aids [H] 1.C.04.a Visual Communication and Identification [H] 1.C.04.a Information Portrayal [H] 1.C.04.a Visually Coupled Interface Design [H] 1.C.04.b Alternative Control and Display Integration [H] 1.C.04.b Direct Sensory Stimulation Development [H] 1.C.05.a Virtual Reality Display for Windowless Cockpit/Synthetic Vision [H] 1.C.05.b Full Color Binocular Helmet-Mounted Display [H] 1.C.05.b Panoramic Night Vision Goggle [H] 1.C.05.b Helmet-Mounted Sight Plus [H] 2.A.01 (1 of 2) Automation of Operator Tasks [H] 3.B.1 (2 of 3) Laser Imaging Radar
14. Metabolic sensors	—
15. Real-time disease and injury surveillance	—
16. Analgesia without CNS depression	—

**Table A-6. Military Needs/USAF R&D Programs Correlation Matrix (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Relevant USAF Program</b>
17. Collective protective system	[H] 4.c.01 Active Noise Reduction Field Measurement [H] 4.c.02 Noise Mitigation
18. Detect/alert/ID systems (required to link into the Medical Planning System)	–
19. Real-time training	[H] 1.A.03 Real-time Workload Classifier – Physiological [H] 1.A.03 Real-time Workload Evaluator – Performance
20. Locator	–
21. Rapid field diagnostics (dipstick for malaria)	–
22. Individual self-decontamination	–
23. Personnel decontamination, isolation, and evacuation	–
24. Blood clotting material/wound repair	[H] 1.B.02 Evacuation Hyperbaric Stretcher [H] 3.A.2 (3 of 4) Hyperbaric Rx Study
25. Host responsive modulation	–
26. Psychological maintenance and augmentation	[H] 1.A.01 Circadian Disruption Countermeasures [H] 1.A.05 Pharmacological Ops Aids [H] 1.A.05 Fatigue Management System
27. Small MRI system	–
28. Minimize physiological effects of injury	1.B.01.a Escape System Restraint Studies
29. Advanced screening/profiling	–
30. Distributed decision-making	[H] 2.A.01 (1 of 2) Distributed Team Performance Testbed [H] 2.A.01 (1 of 2) Team Performance Metrics [H] 2.A.03 (1 of 2) Distributed Sim-based Training Environment [H] 2.B.01 (3 of 3) Command and Control Training Effectiveness
31. Readiness tracker	–
32. Add-on PSM for status of forward-deployed personnel	–
33. Spatial re-orienter	[H] 1.A.06 Advanced Helmet-Mounted Display Symbology [H] 1.A.06 Virtual Interface of Orientational Information
34. Recyclable decontamination agent	–
35. Biodosimetry to assess/permit medical triage	[H] 3.B.1 (3 of 3) Bioaerosol Particle Detection
36. Power/fuel cells	–

**Note 1 for Table A-6:** See Table A-1.

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
1. Personal protective system	K. Biomaterials	Individual protective equipment (Code MTD11)	–	High-altitude protection; life-support equipment; physiological and cognitive limitations; human modeling for system design; crew oxygen systems; active and enhanced noise reduction
2. Multi-component, multi-valent vaccination system	P. Increased disease resistance	Preventive medicine (Code CSS06)	Operational Medicine – Prevention (Code 4)	–
3. Substitute blood	S. Blood substitutes and biocompatible clotting matrices	Combat health logistics system and blood management (Code CSS11)	Operational Medicine – Treatment (Code 5)	–
4. Real-time, integrated alert/detection and identification system	I. Sensors/molecular recognition V. Biomarkers for toxicant/stress exposure	Sensors for mounted forces (Code MTD19)	–	Information warfare
5. Integrate medical into C2 architecture	J. Biomedical imaging and automation	Medical C4I (Code CSS05)	Operational Medicine – Assessment and Detection (Code 2)	Aeromedical evacuation
6. Enhanced prophylaxis and therapeutic agents	P. Increased disease resistance V. Biomarkers for toxicant/stress exposure	Preventive medicine (Code CSS06) Provision of combat support in CB environment (Code CSS13)	Combat Casualty Care – Delivery and Treatment (Code 3) Operational Medicine – Treatment (Code 5)	High workload on task aircrew
7. Distributed medicine	J. Biomedical imaging and automation V. Biomarkers for toxicant/stress exposure	Medical C4I (Code CSS05)	–	Human sensory feedback for telepresence; cognition and performance modeling; sensory systems (AFOSR); perception and cognition (AFOSR)

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
8. Performance enhancing drugs/diet/equipment	A. Recognition/perception B. Memory C. Visual/auditory/olfactory G. Human performance maximization V. Biomarkers for toxicant/stress exposure	Combat stress control (Code CSS14)	—	Accommodation of aircrew in the cockpit; maneuverability; human modeling for system designs; advanced life-support systems; virtual interface technologies; HMDs; aerospace ophthalmologic standards; aerospace neuropsychiatric standards; aerospace visual appliances; enhanced crew performance in sustained operations; chronobiology and neural adaptation (AFOSR); perception and cognition (AFOSR)
9. Laser defensive system	K. Biomaterials	—	—	Optical radiation; personnel protection
10. Non-invasive diagnostics	F. Brain imaging I. Sensors/molecular recognition J. Biomedical imaging and automation N. Pathogen Genome Project	Treatment of battlefield wounds and disease (Code CSS07)	Combat Casualty Care – Casualty Management (Code 1)	Aerospace optical and visual appliances; perception and cognition (AFOSR)
11. Safe water supply	U. Water purification	—	Operational Medicine – Assessment and Detection (Code 2)  Operational Medicine – Treatment (Code 5)	Biological treatment technologies; chemical treatment technologies

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
12. Enhanced physical/ psychological training	G. Human performance maximization	Training support (Code CSS24)  Training and leader development (Code DBS26)  Train leadership skills (Code TRD02)	–	Advanced life-support systems; cognition and performance modeling; force development technology; instructional design and intelligent training; technology for global applications; warfighter training effectiveness behavioral research; night vision device training technology development; aerospace audiologic and vestibular standards; gender-specific physiologic optimization chronobiology and neural adaptation (AFOSR); perception and cognition (AFOSR)
13. Information pre-processing/data fusion and information display	C. Visual/auditory/olfactory	–	–	Crew-centered design tools and processes; enhanced crew performance in sustained operations; 3-D audio displays; night vision technology; human sensory feedback for telepresences; virtual interface technologies; helmet-mounted interface cognition and performance modeling; aerospace optical and visual appliance chronobiology and neural adaptation (AFOSR); sensors systems (AFOSR); perception and cognition (AFOSR)
14. Metabolic sensors	I. Sensors/molecular recognition	Medical C4I (Code CSS05)  Provision of combat support in CB environment (Code CSS13)  Combat stress control (Code CSS14)	Operational Medicine – Prevention (Code 4)	–

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
15. Real-time disease and injury surveillance	F. Brain imaging I. Sensor/molecular recognition V. Biomarkers for toxicant/stress exposure	Treatment of battlefield wounds and disease (Code CSS07)  Far-forward surgical support (Code CSS08)  Battlefield hospitalization (Code CSS09)	Combat Casualty Care – Delivery and Treatment (Code 3)  Operational Medicine – Prevention (Code 4)	–
16. Analgesia without CNS depression	G. Human performance maximization	Far-forward surgical support (Codes CSS08)	Combat Casualty Care – Delivery and Treatment (Code 3)	–
17. Collective protective system	I. Sensor/molecular recognition K. Biomaterials M. Human Genome Project P. Increased disease resistance T. Locator of persons	Soldier/equipment protection (Code EEL08)	–	Aircraft noise modeling and measurement; aircraft noise effects and mitigation
18. Detect/alert/ID systems (required to link into the Medical Planning System)	I. Sensors/molecular recognition J. Biomedical imaging and automation T. Locator of persons	Medical C4I (Code CSS05)	Operational Medicine – Assessment and Detection (Code 2)	–
19. Real-time training	A. Recognition/perception B. Memory C. Visual/auditory/olfactory D. Cognition E. Electrophysiological monitor and brain activity F. Brain imaging G. Human performance maximization	Training support (Code CSS24)  Training and leader development (Code DBS26)  Battle planning and rehearsal (Code MDT17)	–	Human performance assessment

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
20. Locator	I. Sensors/molecular recognition T. Locator of persons	Real-time, on-board, all-weather precision terrain locator (Code DSA07)	–	–
21. Rapid field diagnostics (dipstick for malaria)	I. Sensors/molecular recognition	Treatment of battlefield wounds and disease (Code CSS07)  Provision of combat support in CB environment (Code CSS13)	Operational Medicine – Assessment and Detection (Code 2)	–
22. Individual self-decontamination	I. Sensors/molecular recognition K. Biomaterials L. Encapsulation	NBC DECON (Code MTD13)	–	–
23. Personnel decontamination, isolation, and evacuation	I. Sensors/molecular recognition K. Biomaterials L. Encapsulation P. Increased disease resistance	NBC DECON (Code MTD13)	–	–
24. Blood clotting material/wound repair	S. Blood substitutes and biocompatible clotting matrices	Far-forward surgical support (Code CSS08)	Combat Casualty Care – Casualty Management (Code 1)	Aeromedical evacuation; aerospace ophthalmologic standards
25. Host responsive modulation	C. Visual/auditory/olfactory E. Electrophysiological monitor and brain activity G. Human performance maximization	–	–	–

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
26. Psychological maintenance and augmentation	A. Recognition/perception B. Memory C. Visual/auditory/olfactory D. Cognition E. Electrophysiological monitor and brain activity V. Biomarkers for toxicant/stress exposure	Combat stress control (Code CSS14)	–	Life-support equipment; enhanced crew performance; sustained operations; chronobiology and neural adaptation (AFOSR)
27. Small MRI system	F. Brain imaging	Treatment of battlefield wounds and disease (Code CSS07)	Operational Medicine – Assessment and Detection (Code 2)	–
28. Minimize physiological effects of injury	F. Brain imaging S. Blood substitutes and biocompatible clotting matrices T. Locator of persons	Treatment of battlefield wounds and disease (Code CSS07)	–	Escape system technology; chronobiology and neural adaptation (AFOSR)
29. Advanced screening/profiling	A. Recognition/perception B. Memory C. Visual/auditory/olfactory D. Cognition E. Electrophysiological monitor and brain activity G. Human performance maximization M. Human Genome Project	Commander and battlestaff training (Code BC23) Train leadership skills (Code TRD02)	–	–

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
30. Distributed decision making	C. Visual/auditory/olfactory D. Cognition E. Electrophysiological monitor and brain activity G. Human performance maximization	Medical C4I (Code CSS05)	–	Cognition and performance modeling; technologies for global applications; warfighter training effectiveness behavioral research; chronobiology and neural adaptation (AFOSR); sensory systems (AFOSR); perception and cognition (AFOSR)
31. Readiness tracker	E. Electrophysiological monitor and brain activity F. Brain imaging V. Biomarkers for toxicant/stress exposure	Medical C4I (Code CSS05)	–	–
32. Add-on to PSM for status of forward-deployed personnel	I. Sensors/molecular recognition	NBC DECON (Code MTD13)	–	–
33. Spatial re-orienter	C. Visual/auditory/olfactory E. Electrophysiological monitor and brain activity	–	Combat Casualty Care – Casualty Management (Code 1)	Spatial disorientation countermeasures; chronobiology and neural adaptation (AFOSR); sensory systems (AFOSR); perception and cognition (AFOSR)
34. Recyclable decontamination agent	I. Sensors/molecular recognition J. Biomedical imaging and automation K. Biomaterials L. Encapsulation	NBC DECON (Code MTD13)	–	–

**Table A-7. Comparison of the Military Service Needs and Bio-Tech Developing Technologies (Continued)**

<b>Military Needs <sup>1</sup></b>	<b>Developing Biotechnology Items <sup>2</sup></b>	<b>USA TRADOC Item/Code <sup>3</sup></b>	<b>Navy S&amp;T Item/Code <sup>4</sup></b>	<b>Air Force R&amp;D Programs <sup>5</sup></b>
35. Biodosimetry capability to assess/permit medical triage	I. Sensors/molecular recognition J. Biomedical imaging and automation V. Biomarkers for toxicant/stress exposure	Medical C4I (Code CSS05) Provision of combat support in CB environment (Code CSS13)	Operational Medicine – Assessment and Detection (Code 2)	Aerospace optical and visual appliances
36. Power/fuel cells	H. Nanofabrication K. Biomaterials	Power source and accessories (Code CSS19) Power generation (Code MTD06)	–	–

**Note 1 for Table A-7:** See Table 3.0-1.

**Note 2 for Table A-7:** See Table A-1.

**Note 3 for Table A-7:** See Tables A-2 and A-3.

**Note 4 for Table A-7:** See Tables A-4 and A-5.

**Note 5 for Table A-7:** The Air Force R&D Programs listed in Column 6 are Air Force Research Laboratory (AFRL) programs. The 6.1 programs are noted AFSOR (Air Force Office of Scientific Research). These programs reference the Major Technology Thrust designation in the FY98 Human Systems Technology Area Plan.

## **APPENDIX B.**

### **BIOSAFETY LEVELS**

#### ***INTRODUCTION***

The formal definition for each of the four biosafety levels is sometimes elusive or incomplete; however, at times, this definition is important for clarity of contracts, standards, international agreements, and other matters. The definitions and criteria presented in this appendix are extracted from the National Institute of Health (NIH) as an authoritative reference. However, variations exist that may or may not affect specific applications.

## **APPENDIX B.**

### **BIOSAFETY LEVELS**

BIOSAFETY LEVEL 4 is required for work with dangerous and exotic agents that pose a high individual risk of aerosol-transmitted laboratory infections and life-threatening disease. Agents with a close or identical antigenic relationship to Biosafety Level 4 agents are handled at this level until sufficient data are obtained to confirm continued work at this level or to work with these agents at a lower level.

Members of the laboratory staff have specific and thorough training in handling extremely hazardous infectious agents, and they understand the primary and secondary containment functions of the standard and special practices, the containment equipment, and the laboratory design characteristics. They are supervised by competent scientists who are trained and experienced in working with these agents. The laboratory director strictly controls access to the laboratory. The facility is either in a separate building or in a controlled area within a building—an area that is completely isolated from all other areas of the building. A specific facility operations manual is prepared or adopted.

Within work areas of the facility, all activities are confined to Class III Biosafety Cabinets (BSCs) or Class II BSCs used with one-piece positive pressure personnel suits ventilated by a life-support system. The Biosafety Level 4 laboratory has special engineering and design features to prevent microorganisms from being disseminated into the environment.

The following standard and special safety practices, equipment, and facilities apply to agents assigned to Biosafety Level 4.

#### **A. STANDARD MICROBIOLOGICAL PRACTICES**

1. Access to the laboratory is limited or restricted at the discretion of the laboratory director when experiments are in progress.
2. Persons must wash their hands after handling infectious materials and animals, and they take a decontaminating shower when they leave the laboratory.
3. Eating, drinking, smoking, handling contact lenses, and applying cosmetics are not permitted in the laboratory. Persons who wear contact lenses in laboratories should also wear goggles or a face shield. Food is stored outside the work area in cabinets or refrigerators designated for this purpose only.

4. Mouth pipetting is prohibited. Only mechanical pipetting devices are used.
5. All procedures are performed carefully to minimize the creation of aerosols.
6. Work surfaces are decontaminated at least once a day and after any spill of viable material.
7. An insect and rodent control program is in effect.

#### **B. SPECIAL PRACTICES**

1. Only persons whose presence in the facility or individual laboratory rooms is required for program or support purposes are authorized to enter. Persons who are immunocompromised or immunosuppressed may be at risk of acquiring infections. Therefore, persons who may be at increased risk of acquiring infection or for whom infection may be unusually hazardous (e.g., children or pregnant women) are not allowed in the laboratory or animal rooms.

The supervisor has the final responsibility for assessing each circumstance and determining who may enter or work in the laboratory. Access to the facility is limited by means of secure, locked doors. Accessibility is managed by the laboratory director, biohazards control officer, or other person responsible for the physical security of the facility. Before entering, persons are advised of the potential biohazards and instructed about appropriate safeguards for ensuring their safety. Authorized persons must comply with the instructions and all other applicable entry and exit procedures. A log book, signed by all personnel, indicates the date and time of each entry and exit. Practical and effective protocols for emergency situations are established.

2. When infectious materials or infected animals are present in the laboratory or animal rooms, hazard warning signs, incorporating the universal biohazard symbol, are posted on all access doors. The sign identifies the agent, lists the name of the laboratory director or other responsible person(s), and indicates any special requirements for entering the area (e.g., the need for immunizations or respirators).

3. The laboratory director is responsible for ensuring that all personnel demonstrate a high proficiency in standard microbiological practices and techniques and in the special practices and operations specific to the laboratory facility *before* working with organisms at Biosafety Level 4. This might include prior experience in handling human pathogens or cell cultures or specific training provided by the laboratory director or other competent scientists proficient in these unique safe microbiological practices and techniques.
4. Laboratory personnel receive available immunizations for the agents handled or potentially present in the laboratory.
5. Baseline serum samples for all laboratory and other at-risk personnel are collected and stored. Additional serum specimens may be collected periodically, depending on the agents handled or the function of the laboratory. The decision to establish a serologic surveillance program takes into account the availability of methods for the assessment of antibody to the agent(s) of concern. The program provides for the testing of serum samples at each collection interval and the communication of results to the participants.
6. A biosafety manual is prepared or adopted. Personnel are advised of special hazards and are required to read and to follow instructions on practices and procedures.
7. Laboratory personnel receive appropriate training on the potential hazards associated with the work involved, the necessary precautions to prevent exposures, and the exposure evaluation procedures. Personnel receive annual updates or additional training, as necessary, for procedural changes.
8. Personnel enter and leave the facility only through the clothing change and shower rooms and shower each time they leave the facility. Personnel use the airlocks to enter or leave the laboratory only in an emergency.
9. Personal clothing is removed in the outer clothing change room and kept there. Complete laboratory clothing, including undergarments, pants, shirts or jumpsuits, shoes, and gloves, is provided and used by all personnel entering the facility. When leaving the laboratory and before proceeding into the shower area, personnel remove their laboratory clothing in the inner change room. Soiled clothing is autoclaved before laundering.
10. Supplies and materials needed in the facility are brought in by way of the double-doored autoclave, fumigation chamber, or airlock, which is appropriately decontaminated between each use. After securing the outer doors, personnel within the facility retrieve the materials by opening the interior doors of the autoclave, fumigation chamber, or airlock. These doors are secured after materials are brought into the facility.
11. A high degree of precaution must always be taken with any contaminated sharp items, including needles and syringes, slides, pipettes, capillary tubes, and scalpels. Needles and syringes or other sharp instruments are restricted in the laboratory for use only when there is no alternative, such as for parenteral injection, phlebotomy, or aspiration of fluids from laboratory animals and diaphragm bottles. Plasticware should be substituted for glassware whenever possible.
  - a. Only needle-locking syringes or disposable syringe-needle units (i.e., needle is integral to the syringe) are used for injection or aspiration of infectious materials. Used disposable needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal; rather, they must be carefully placed in conveniently located puncture-resistant containers used for sharps disposal. Non-disposable sharps must be placed in a hard-walled container for transport to a processing area for decontamination, preferably by autoclaving.
  - b. Syringes that re-sheath the needle, needle-less systems, and other safe devices should be used when appropriate.
  - c. Broken glassware must not be handled directly by hand but must be removed by mechanical means (e.g., a brush and dustpan, tongs, or forceps). Containers of contaminated needles, sharp equipment, and broken glass should be decontaminated before disposal, according to any local, state, or federal regulations.
12. Biological materials to be removed from the Class III BSC or from the Biosafety Level 4 laboratory in a viable or intact state are transferred to a non-breakable, sealed primary container and then enclosed in a non-breakable, sealed secondary container. This container is removed from the facility through a disinfectant dunk tank, fumigation chamber, or an airlock designed for this purpose.
13. No materials, except for biological materials that are to remain in a viable or intact state, are removed from the Biosafety Level 4 laboratory unless they have been autoclaved or decontaminated before they leave the facility. Equipment or material that might be damaged by high temperatures or steam may be decontaminated by gaseous or vapor methods in an airlock or chamber designed for this purpose.
14. Laboratory equipment is decontaminated routinely after work with infectious materials is finished and especially after overt spills, splashes, or

other contamination with infectious materials. Contaminated equipment should also be decontaminated before it is sent for repair or maintenance.

15. Spills of infectious materials are contained and cleaned up by appropriate professional staff or others properly trained and equipped to work with concentrated infectious material.
16. A system is set up for reporting laboratory accidents/exposures and employee absenteeism and for the medical surveillance of potential laboratory-associated illnesses. Written records are prepared and maintained. An essential adjunct to such a reporting-surveillance system is the availability of a facility for the quarantine, isolation, and medical care of personnel with potential or known laboratory-associated illnesses.
17. Materials (e.g., plants, animals, and clothing) not related to the experiment being conducted are not permitted in the facility.

#### **C. SAFETY EQUIPMENT (PRIMARY BARRIERS)**

1. All procedures within a facility with agents assigned to Biosafety Level 4 are conducted in the Class III BSCs or in Class II BSCs used in conjunction with one-piece positive pressure personnel suits ventilated by a life-support system.

Activities with viral agents that require Biosafety Level 4 secondary containment capabilities can be conducted within Class II BSCs within the facility, without the one-piece positive pressure personnel suit being used if (a) the facility has been decontaminated, (b) no work is being conducted in the facility with other agents assigned to Biosafety Level 4, (c) all personnel are immunized against the specific agent being manipulated and demonstrate protective antibody levels, and (d) all other standard and special practices are followed.

2. All personnel entering the facility will don complete laboratory clothing, including undergarments, pants, shirts or jumpsuits, shoes, and gloves. All such personal protective equipment is removed in the change room before showering and leaving the laboratory.

#### **D. LABORATORY FACILITY (SECONDARY BARRIERS)**

1. The Biosafety Level 4 facility consists of either a separate building or a clearly demarcated and isolated zone within a building. Outer and inner change rooms, separated by a shower, are provided for personnel entering and leaving the facility. A double-doored autoclave, fumigation chamber, or ventilated airlock is provided for passage of those materials, supplies,

or equipment that are not brought into the facility through the change room.

2. Walls, floors, and ceilings of the facility are constructed to form a sealed internal shell that facilitates fumigation and is animal and insect proof. The internal surfaces of this shell are resistant to liquids and chemicals, thus facilitating cleaning and decontamination of the area. All penetrations in these structures and surfaces are sealed. Any drains in the floors contain traps filled with a chemical disinfectant of demonstrated efficacy against the target agent, and they are connected directly to the liquid waste decontamination system. Sewer vents and other ventilation lines contain high-efficiency particulate air (HEPA) filters.
3. Internal facility appurtenances (e.g., light fixtures, air ducts, and utility pipes) are arranged to minimize the horizontal surface area on which dust can settle.
4. Bench tops have seamless surfaces that are impervious to water and resistant to acids, alkalis, organic solvents, and moderate heat.
5. Laboratory furniture is of simple and sturdy construction, and spaces between benches, cabinets, and equipment are accessible for cleaning.
6. A foot-, elbow-, or automatically operated handwashing sink is provided near the door of each laboratory room in the facility.
7. If there is a central vacuum system, it does not serve areas outside the facility. In-line HEPA filters are placed as near as practicable to each use point or service cock. Filters are installed to permit in-place decontamination and replacement. Other liquid and gas services to the facility are protected by devices that prevent backflow.
8. If water fountains are provided, they are foot operated and are located in the facility corridors outside the laboratory. The water service to the fountain is not connected to the backflow-protected distribution system supplying water to the laboratory areas.
9. Access doors to the laboratory are self-closing and lockable.
10. Any windows are breakage resistant.
11. A double-doored autoclave is provided for decontaminating materials passing out of the facility. The autoclave door that opens to the area external to the facility is sealed to the outer wall and automatically controlled so that the outside door can be opened only after the autoclave "sterilization" cycle has been completed.
12. A pass-through dunk tank, fumigation chamber, or an equivalent decontamination method is provided so that materials and equipment that

cannot be decontaminated in the autoclave can be safely removed from the facility.

13. Liquid effluents from laboratory sinks, BSCs, floor drains (if used), and autoclave chambers are decontaminated by heat treatment before being discharged to the sanitary sewer. Effluents from showers and toilets can be discharged to the sanitary sewer without treatment. The process used for decontamination of liquid wastes must be validated physically and biologically by use of a constant recording temperature sensor in conjunction with an indicator microorganism that has a defined heat susceptibility profile.
14. A dedicated non-recirculating ventilation system is provided. The supply and exhaust components of the system are balanced to ensure directional airflow from the area of least hazard to the area(s) of greatest potential hazard. The differential pressure/directional airflow between adjacent areas is monitored and alarmed to indicate malfunction of the system. The airflow in the supply and exhaust components is monitored and the components interlocked to ensure that inward (or zero) airflow is maintained.
15. The general room exhaust air from a facility in which the work is conducted in a Class III BSC system is treated by a passage through a HEPA filter(s) before being discharge to the outside. The air is discharged away from occupied spaces and air intakes. The HEPA filter(s) is located as near as practicable to the source to minimize the length of potentially contaminated ductwork. The HEPA filter housings are designed to allow for in situ decontamination of the filter before removal or removal of the filter in a sealed gas-tight primary container for subsequent decontamination and/or destruction by incineration.

The design of the HEPA filter housing should facilitate validation of the filter installation. The use of pre-certified HEPA filters can be an advantage. The service-life of the exhaust HEPA filters can be extended through adequate filtration of the supply air.

16. A specially designed suit area may be provided in the facility to provide personnel protection equivalent to that provided by Class III BSCs. Personnel who enter this area wear a one-piece positive pressure suit that is ventilated by a life-support system. The life-support system includes alarms and emergency backup breathing air tanks. Entry to this area is through an airlock that is fitted with airtight doors. A chemical shower is provided to decontaminate the surface of the suit before the worker leaves the area. The exhaust air from the suit area is filtered by two sets of HEPA filters installed in series. A duplicate filtration unit, exhaust fan, and an automatically starting emergency power source are provided. The

air pressure within the suit area is lower than that of any adjacent area. Emergency lighting and communication systems are provided. All penetrations into the internal shell of the suit area are sealed. A double-doored autoclave is provided for decontaminating waste materials to be removed from the suit area.

17. The treated exhaust air from Class II BSCs, located in a facility in which workers wear a positive pressure suit, can be discharged into the animal room environment or to the outside through the facility air exhaust system. The BSCs are tested and certified at 12-month intervals. The air exhausted from Class III BSCs is passed through two HEPA filter systems (in series) before being discharged to the outside.

If the treated exhaust is discharged to the outside through the facility exhaust system, it is connected to this system in a manner that avoids any interference with the air balance of the cabinets or the facility exhaust system.

BIOSAFETY LEVEL 3 is applicable to clinical, diagnostic, teaching, research, or production facilities in which work is done with indigenous or exotic agents that may cause serious or potentially lethal disease as a result of exposure by inhalation. Laboratory personnel have specific training in handling pathogenic and potentially lethal agents and are supervised by competent scientists who are experienced in working with these agents.

All procedures involving the manipulation of infectious materials are conducted within BSCs or other physical containment devices or by personnel wearing appropriate personal protective clothing and equipment. The laboratory has special engineering and design features.

Many existing facilities may not have all the facility safeguards recommended for Biosafety Level 3 (e.g., access zone, sealed penetrations, and directional airflow, and so forth). In these circumstances, acceptable safety may be achieved for routine or repetitive operations (e.g., diagnostic procedures involving the propagation of an agent for identification, typing, and susceptibility testing) in Biosafety Level 2 facilities. However, the recommended Standard Microbiological Practices, Special Practices, and Safety Equipment for Biosafety Level 3 must be rigorously followed. The decision to implement this modification of Biosafety Level 3 recommendations should be made only by the laboratory director.

The following standard and special safety practices, equipment, and facilities apply to agents assigned to Biosafety Level 3.

#### **A. STANDARD MICROBIOLOGICAL PRACTICES**

1. Access to the laboratory is limited or restricted at the discretion of the laboratory director when experiments are in progress.
2. Persons must wash their hands after handling infectious materials and animals, after removing gloves, and when they leave the laboratory.
3. Eating, drinking, smoking, handling contact lenses, and applying cosmetics are not permitted in the laboratory. Persons who wear contact lenses in laboratories should also wear goggles or a face shield. Food is stored outside the work area in cabinets or refrigerators designated for this purpose only.
4. Mouth pipetting is prohibited. Mechanical pipetting devices are used.
5. All procedures are performed carefully to minimize the creation of aerosols.
6. Work surfaces are decontaminated at least once a day and after any spill of viable material.
7. All cultures, stocks, and other regulated wastes are decontaminated before disposal by an approved decontamination method (e.g.,

autoclaving). Materials to be decontaminated outside of the immediate laboratory are to be placed in a durable, leakproof container and closed for transport from the laboratory. Materials to be decontaminated at an off-site location are packaged in accordance with applicable local, state, and federal regulations before being removed from the facility.

8. An insect and rodent control program is in effect.

#### **B. SPECIAL PRACTICES**

1. Laboratory doors are kept closed when experiments are in progress.
2. The laboratory director controls access to the laboratory and restricts access to persons whose presence is required for program or support purposes. For example, persons who are immunocompromised or immunosuppressed may be at risk of acquiring infections. Persons who are at increased risk of acquiring infection or for whom infection may be unusually hazardous are not allowed in the laboratory or animal rooms.
3. The laboratory director establishes policies and procedures whereby only persons who have been advised of the potential biohazard, who meet any specific entry requirements (e.g., immunization), and who comply with all entry and exit procedures can enter the laboratory or animal rooms.
4. When infectious materials or infected animals are present in the laboratory or containment module, a hazard warning sign, incorporating the universal biohazard symbol, is posted on all laboratory and animal room access doors. The hazard warning sign identifies the agent, lists the name and telephone number of the laboratory director or other responsible person(s), and indicates any special requirements for entering the laboratory (e.g., the need for immunizations, respirators, or other personal protective measures).
5. Laboratory personnel receive the appropriate immunizations or tests for the agents handled or potentially present in the laboratory [e.g., hepatitis B vaccine or tuberculosis (TB) skin testing].
6. Baseline serum samples are collected and stored for all laboratory and other at-risk personnel. Additional serum specimens may be collected periodically, depending on the agents handled or the function of the laboratory.
7. A biosafety manual is prepared or adopted. Personnel are advised of special hazards and are required to read and to follow instructions on practices and procedures.
8. Laboratory personnel receive appropriate training on the potential hazards associated with the work involved, the necessary precautions to prevent

exposures, and the exposure evaluation procedures. Personnel receive annual updates or additional training, as necessary, for procedural changes.

9. The laboratory director is responsible for ensuring that all personnel demonstrate proficiency in standard microbiological practices and techniques and in the practices and operations specific to the laboratory facility *before* working with organisms at Biosafety Level 3. This might include prior experience in handling human pathogens or cell cultures or specific training provided by the laboratory director or other competent scientists proficient in safe microbiological practices and techniques.
10. A high degree of precaution must always be taken with any contaminated sharp items, including needles and syringes, slides, pipettes, capillary tubes, and scalpels. Needles and syringes or other sharp instruments should be restricted in the laboratory for use only when there is no alternative, such as for parenteral injection, phlebotomy, or aspiration of fluids from laboratory animals and diaphragm bottles. Plasticware should be substituted for glassware whenever possible.
  - a. Only needle-locking syringes or disposable syringe-needle units (i.e., needle is integral to the syringe) are used for injection or aspiration of infectious materials. Used disposable needles must not be bent, sheared, broken, recapped, removed from disposable syringes, or otherwise manipulated by hand before disposal; rather, they must be carefully placed in conveniently located puncture-resistant containers used for sharps disposal. Non-disposable sharps must be placed in a hard-walled container for transport to a processing area for decontamination, preferably by autoclaving.
  - b. Syringes that re-sheath the needle, needle-less systems, and other safe devices should be used when appropriate.
  - c. Broken glassware must not be handled directly by hand but must be removed by mechanical means (e.g., a brush and dustpan, tongs, or forceps). Containers of contaminated needles, sharp equipment, and broken glass should be decontaminated before disposal, according to any local, state, or federal regulations.
11. All manipulations involving infectious materials are conducted in BSCs or other physical containment devices within the containment module. No work in open vessels is conducted on the open bench.
12. Laboratory equipment and work surfaces should be decontaminated with an appropriate disinfectant on a routine basis, after work with infectious materials is finished, and especially after overt spills, splashes, or other contamination with infectious materials. Contaminated equipment should

also be decontaminated before it is sent for repair or maintenance or packaged for transport in accordance with applicable local, state, or federal regulations.

13. Cultures, tissues, or specimens of body fluids are placed in a container that prevents leakage during collection, handling, processing, storage, transport, or shipping.
14. All potentially contaminated waste materials (e.g., gloves, lab coats, and so forth) from laboratories or animal rooms are decontaminated before disposal or reuse.
15. Spills of infectious materials are decontaminated, contained, and cleaned up by appropriate professional staff or others properly trained and equipped to work with concentrated infectious material. Plastic-backed paper toweling used for clean-up on non-perforated work surfaces within BSCs facilitates.
16. Spills and accidents that result in overt or potential exposures to infectious materials are immediately reported to the laboratory director. Appropriate medical evaluation, surveillance, and treatment are provided and written records are maintained.
17. Animals and plants not related to the work being conducted are not permitted in the laboratory.

### C. SAFETY EQUIPMENT (PRIMARY BARRIERS)

1. Properly maintained BSCs (Class II or III) are used for all manipulation of infectious materials.
2. Outside of a BSC, appropriate combinations of personal protective equipment are used (e.g., special protective clothing, masks, gloves, face protection, or respirators), in combination with physical containment devices (e.g., centrifuge safety cups, sealed centrifuge rotors, or containment caging for animals).
3. This equipment must be used for manipulations of cultures and of those clinical or environmental materials that may be a source of infectious aerosols, the aerosol challenge of experimental animals, harvesting of tissues or fluids from infected animals and embryonated eggs, and necropsy of infected animals.
4. Face protection (goggles and mask or a face shield) is worn for manipulations of infectious materials outside of a BSC.
5. Respiratory protection is worn when aerosols cannot be safely contained (i.e., outside of a BSC) and in rooms containing infected animals.

6. Protective laboratory clothing (e.g., solid-front or wrap-around gowns, scrub suits, or coveralls) must be worn inside—but not outside—the laboratory. Reusable laboratory clothing is to be decontaminated before being laundered.
7. Gloves must be worn when handling infected animals and when hands may contact infectious materials and contaminated surfaces or equipment. Disposable gloves should be discarded when contaminated—and never washed for reuse.

#### ***D. LABORATORY FACILITIES (SECONDARY BARRIERS)***

1. The laboratory is separated from areas that are open to unrestricted traffic flow within the building. Passage through two sets of self-closing doors is the basic requirement for entry into the laboratory from access corridors or other contiguous areas. A clothes change room (shower optional) may be included in the passage way.
2. Each laboratory contains a foot-, elbow-, or automatically operated sink for hand washing. This sink is located near the laboratory exit door.
3. The interior surfaces of walls, floors, and ceilings are water resistant so that they can be easily cleaned. Penetrations in these surfaces are sealed or are capable of being sealed to facilitate decontamination.
4. Bench tops are impervious to water and resistant to acids, alkalis, organic solvents, and moderate heat.
5. Laboratory furniture is sturdy, and spaces between benches, cabinets, and equipment are accessible for cleaning.
6. Windows in the laboratory are closed and sealed.
7. A method for decontaminating all laboratory wastes is available, preferably within the laboratory (i.e., autoclave, chemical disinfection, incineration, or other approved decontamination method).
8. A ducted exhaust air ventilation system is provided. This system creates directional airflow that draws air from “clean” areas into the laboratory toward “contaminated” areas. The exhaust air is not recirculated to any other area of the building and is discharged to the outside with filtration or other optional treatment. The outside exhaust must be dispersed away from occupied areas and air intakes. Laboratory personnel must verify that the direction of the airflow (into the laboratory) is proper.
9. The HEPA-filtered exhaust air from Class II or Class III BSCs is discharged directly to the outside or through the building exhaust system. If the HEPA-filtered exhaust air from Class II or III BSCs is to be discharged to the outside through the building exhaust air system, it is

connected to this system in a manner (e.g., thimble unit connection) that avoids any interference with the air balance of the cabinets or building exhaust system. Exhaust air from Class II BSCs can be recirculated within the laboratory if the cabinet is tested and certified at least every 12 months.

10. Continuous flow centrifuges or other equipment that may produce aerosols are contained in devices that exhaust air through HEPA filters before discharge into the laboratory.
11. Vacuum lines are protected with liquid disinfectant traps and HEPA filters, or their equivalent, which are routinely maintained and replaced as needed.
12. An eyewash facility is readily available.

BIOSAFETY LEVEL 2 is similar to Level 1 and is suitable for work involving agents of moderate potential hazard to personnel and the environment. It differs in that (1) laboratory personnel have specific training in handling pathogenic agents and are directed by competent scientists, (2) access to the laboratory is limited when work is being conducted, (3) extreme precautions are taken with contaminated sharp items, and (4) certain procedures in which infectious aerosols or splashes may be created are conducted in BSCs or other physical containment equipment.

BIOSAFETY LEVEL 1 is not suitable for working with toxic or hazardous substances.